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UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

OTSUKA PHARMACEUTICAL CO., LTD.,

Plaintiff,

v.

SANDOZ, INC., TEVA PHARMACEUTICALS USA, INC., TEVA PHARMACEUTICAL INDUSTRIES LTD., BARR LABORATORIES, INC., BARR PHARMACEUTICALS, INC., APOTEX INC., APOTEX CORP., SUN PHARMACEUTICAL INDUSTRIES, LTD., SYNTHON HOLDING BV, SYNTHON BV, SYNTHON PHARMACEUTICALS, INC., and SYNTHON LABORATORIES, INC.

Defendants.

Consolidated Civil Action No. 3:07-cv-01000 (MLC) (LHG)

Honorable Judge Mary L. Cooper

Magistrate Lois H. Goodman

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DEFENDANTS' REPLY TO OTSUKA'S POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW

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I. THE ASSERTED CLAIMS ARE INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING.

A. THE TESTS FOR STATUTORY OBVIOUSNESS UNDER § 103 AND OBVIOUSNESS-TYPE DOUBLE PATENTING ARE NOT THE SAME.

Otsuka contends that the double patenting analysis in this case is "subsumed" by the obviousness analysis under § 103 because the '416 patent is prior art to the '528 patent-in-suit. (*See* Otsuka's Post-Trial Proposed Findings of Fact and Conclusions of Law ("OFFCL") at 213-17.) The Federal Circuit has recently confirmed however, that the tests for obviousness under § 103 and obviousness-type double patenting are *not* the same. *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009). As the Federal Circuit found in *Procter & Gamble*:

> In general, the obviousness analysis applies to double patenting, except for three distinctions. First, statutory obviousness compares claimed subject matter to the prior art, while non-statutory double patenting compares claims in an earlier patent to claims in a later patent or application. Second, *double patenting does not require inquiry into a motivation to modify the prior art.* Finally, *double patenting does not require inquiry into objective criteria suggesting non-obviousness*.

Id. at 999 (internal citations omitted) (emphasis added).

Otsuka does not even attempt to address the *Procter & Gamble* decision, which is Federal Circuit precedent directly on point. Moreover, Otsuka's attempt to distinguish the Federal Circuit's earlier decision in *Geneva Pharmaceuticals, Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373 (Fed. Cir. 2003), which likewise found that obviousness-type double patenting does not require inquiry into motivation to modify the prior art or objective criteria of non-obviousness, on the ground that the double patenting finding there was based on anticipation and not obviousness fails in light of *Procter & Gamble*. The double patenting issue in *Procter & Gamble*, as in this case, was based on obviousness not anticipation. The district court cases cited

by Otsuka are all earlier than the Federal Circuit's decision in *Procter & Gamble* and, in any event, are not controlling. Thus the Court concludes that obviousness-type double patenting and obviousness must be analyzed separately.

Furthermore, since the double patenting inquiry, unlike the obviousness inquiry under § 103, must begin with the claims of the earlier patent, and does not require inquiry into motivation to modify the prior art, the Court also concludes that Defendants need not prove that a person of ordinary skill would have been motivated to select the unsubstituted butoxy as a "lead compound" in order to establish that the claims of the '528 patent are invalid for obviousness-type double patenting.

B. THE ASSERTED CLAIMS ARE OBVIOUS VARIANTS OF CLAIM 13 OF THE '416 PATENT (THE UNSUBSTITUTED BUTOXY).

1. *The Nakagawa Declaration Is Prior Art.*

Otsuka contends that the Nakagawa Declaration does not qualify as prior art and should not be considered by this Court. (*See* OFFCL at 180-87.) Otsuka, however, does not cite a single case in which a court has declined to consider the contents of a file wrapper of an earlier issued patent in an invalidity analysis on the ground that it was not prior art. On the contrary, three courts that have considered the issue have all found that the contents of a file wrapper of an issued patent qualify as prior art. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007); *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374 (Fed. Cir. 2006); and *Bamberger v. Cheruvu*, 55 U.S.P.Q.2d 1523 (B.P.A.I. 1998). The Court finds that these cases are directly on point and control here. The cases on which Otsuka relies do not address the issue of whether file wrappers should be considered prior art and are therefore not as relevant as *Takeda*, *Bruckelmyer* and *Bamberger* to the issue before the Court.

Otsuka cannot effectively distinguish *Takeda*, *Bruckelmyer* and *Bamberger*. The courts

in *Takeda*, *Bamberger* and *Bruckelmyer* were clear that prosecution histories of issued patents are publicly accessible and must be considered as part of the prior art. *Takeda*, 492 F.3d at 1363 ("Alphapharm asserts that the court excluded the prosecution history of the '779 patent from the scope of the prior art after wrongly concluding that it was not accessible to the public. . . . [W]hile the district court may have incorrectly implied that prosecution histories are not accessible to the public, the court nonetheless considered the prosecution history of the '779 patent in its obviousness analysis . . . any error committed by the court in this regard was harmless error."); *Bamberger*, 55 U.S.P.Q.2d at 1537 n.22 ("We have assumed that the Wellborn declaration in the file of the Wellborn patent is prior art under 35 U.S.C. § 102(b), given that the patent issued more than one year prior to the date Cheruvu filed the application which matured into the Cheruvu patent and a patent file is accessible to the public on the date a patent issue. 37 CFR Section 1.11 (1988)."); *Bruckelmyer*, 445 F.3d at 1378 ("We agree with the district court that the [file wrapper document] was 'publicly accessible,' and thus that it was a 'printed publication' under 35 U.S.C. § 102(b).").

Otsuka asks the Court to disregard the Federal Circuit's decisions in *Takeda* and *Bamberger* based on its characterization of the above findings as dicta. (*See* OFFCL at 183-86.) Otsuka is incorrect. The findings quoted above were integral to the court's decisions in both those cases. In *Takeda* and *Bamberger* the Federal Circuit, the district court, the PTO Board, and all the parties understood that the contents of prosecution histories were being relied upon as prior art. In each case, the court specifically considered these documents in reaching its conclusions on obviousness.

Otsuka does not argue that the holding in *Bruckelmyer* was dictum, but rather that the case is distinguishable on its facts. The Court finds, however, that the facts of *Bruckelmyer* are

indistinguishable from those of this case. In *Bruckelmyer*, as in this case, the prior art at issue was part of the file wrapper of an issued patent. There, as here, the file wrapper was available for public inspection in the appropriate Patent Office (Canada in *Bruckelmyer*, the U.S. here) as of the relevant date, but was not itself indexed. There, as here, the issued patent contained some disclosure that would permit a person of ordinary skill interested in the subject matter and exercising reasonable diligence to locate the contents of the file wrapper. Based on these facts, the Federal Circuit found in *Bruckelmyer* that the contents of the Canadian file wrapper were prior art and was properly used to invalidate the patent at issue in that case. The same is true here.

Otsuka attempts to distinguish *Bruckelmyer* by arguing that the file wrapper document at issue in *Bruckelmyer* was a patent application and the file wrapper at issue here is a declaration. (*See* OFFCL at 184-85.) This is a distinction without a difference. The patent application in *Bruckelmyer* was abandoned, and was accessible only as part of the file wrapper of the issued patent. Nothing in *Bruckelmyer* suggests that the outcome in that case would have been different were the relevant part of the file wrapper a declaration rather than an abandoned application.

Otsuka also claims that the specification of the ’416 patent, unlike that in *Bruckelmyer*, would not have led the interested person of ordinary skill to search for and locate the ’416 patent file wrapper. (*See* OFFCL at 182-83.) But the evidence is to the contrary. The ’416 patent is entitled “Pharmaceutically Useful Carbostyril Derivatives” and the specification specifically states that its compounds are “useful for central nervous controlling agents such as . . . antischizophrenia agents.” (DTX 6, Col. 3:14-17.) As Dr. Press testified, a medicinal chemist would understand from the specification of the ’416 patent that it is directed to carbostyril derivatives that can be used as drugs to treat schizophrenia. (Press 121:1-5.)

2. *The Nakagawa Declaration Teaches the Person of Ordinary Skill to Modify the Unsubstituted Butoxy by Substituting Chlorine at the 2 and 3 Positions.*

Defendants' experts Dr. Press and Dr. Castagnoli provided detailed testimony concerning what the Nakagawa Declaration would teach the person of ordinary skill in the art who was considering modifying the structure of the unsubstituted butoxy to increase antischizophrenic potency. (Press 128:10-17; 134:9-138:4; 140:22-141:10; 158:5-164:10; 164:23-166:15; 166:24-168:2; Castagnoli 663:1-3; 671:8-672:21; 677:4-18; 736:2-737:24; 752:3-15; 785:16-786:124; 799:8-20.) None of Otsuka's experts directly addressed this testimony. In particular, none of Otsuka's experts disputed that the Nakagawa Declaration would teach the person of ordinary skill that: (1) adding a chlorine at the 2 position of the unsubstituted propoxy increases antischizophrenic potency; (2) adding a chlorine at the 3 position of the unsubstituted propoxy increases antischizophrenic potency; (3) adding a chlorine at the 4 position of the unsubstituted propoxy decreases antischizophrenic potency; and (4) the unsubstituted butoxy is a more potent antischizophrenic agent than the unsubstituted propoxy. The credible testimony of Dr. Press and Dr. Castagnoli on these issues is therefore unrebutted.

Otsuka claims that Dr. Castagnoli testified that a person of ordinary skill would add methyl groups rather than chlorines to the unsubstituted butoxy. (*See* OFFCL at 220.) This mischaracterizes Dr. Castagnoli's testimony. Dr. Castagnoli testified clearly that the person of ordinary skill would learn from the Nakagawa Declaration that chlorines should be added at the 2 and 3 positions of the phenyl ring of the unsubstituted butoxy. (Castagnoli 757:15-758:14.)

Otsuka's experts also did not effectively rebut the testimony of Defendants' experts concerning the general medicinal chemistry principles that the person of ordinary skill would apply when analyzing the data in the Nakagawa Declaration. As Dr. Press testified, medicinal chemists operate under the principle that each substituent in a molecule makes an independent

contribution to biological activity and that these contributions can be combined in an additive way. (Press 166:24-168:5.) In this case, as Dr. Press testified, the person of ordinary skill would assume that the addition of chlorine at each of the 2 and 3 positions of the unsubstituted butoxy would lead to increased antischizophrenic potency. Otsuka cites no testimony to the contrary. Otsuka's critiques of Dr. Press's opinions on this issue are attorney argument, not evidence, and are entitled to no weight.

Both Dr. Press and Dr. Castagnoli also testified that a person of ordinary skill would expect that information from the propoxy series of compounds would be applicable to the butoxy series. (Press 137:15-138:4; 98:7-99:16; Castagnoli 735:2-20; 667:23-668:11.) Dr. Castagnoli specifically referenced a standard text called BURGER'S MEDICINAL CHEMISTRY that he has used extensively throughout his career. (Castagnoli 670:1-9; DTX 621.) In a chapter entitled "Guides for Drug and Analog Design," BURGER'S discusses the concept of homologation, which is, for example, converting from a propoxy to a butoxy. BURGER'S states that this systematic approach to structure-activity relationships (SAR) is "as old as organic chemistry itself." In general, an increase in chain length parallels an increase in activity up to a maximum. (DTX 621 at 337.) Dr. Castagnoli's unrebutted testimony was that "the obvious conclusion from what is well-known in the literature . . . is that going from propoxy to butoxy would lead to an enhanced brain concentration of the resulting compound." (Castagnoli 680:13-17.) This testimony was also not addressed by Otsuka's experts.

The arguments that Otsuka has advanced with respect to double patenting are largely irrelevant to the Court's inquiry. As set forth above, Otsuka's principal argument, that one of ordinary skill would not have chosen the unsubstituted butoxy as a lead compound, is irrelevant as a matter of law to the double patenting analysis. (*See* OFFCL at 217-20.) Otsuka also argues

that the purpose of the Nakagawa Declaration was not to compare the compounds of the '416 patent against each other. (*See, e.g.*, OFFCL at 83-85.) But this is beside the point. Regardless of the declaration's purpose, it is undisputed that the declaration provides data from which a person of ordinary skill can make such comparisons.

Otsuka's argument that chlorination is not *required* for antipsychotic activity likewise misses the mark. (*See* OFFCL at 93-95.) The question here is not whether chlorine is always required for antipsychotic activity, but rather, whether the relevant prior art in this case would teach the person of ordinary skill that adding chlorine to the specific compound at issue here, the unsubstituted butoxy, would lead to increased antipsychotic activity. As set forth above, Defendants presented clear and convincing evidence that the Nakagawa Declaration teaches the substitutions that would result in aripiprazole.

Otsuka's contention that Dr. Press's testimony should not be credited because he did not perform testing to support his position is inconsistent with the analysis to be performed by the Court. (*See* OFFCL at 73.) The question before the Court is what one of ordinary skill in the art would learn from the information that was publicly available as of 1988. Dr. Press's testimony was directed to this issue. Any testing he would have performed in 2010 would have been irrelevant to this inquiry.

II. THE ASSERTED CLAIMS ARE INVALID FOR OBVIOUSNESS UNDER 35 U.S.C. § 103.[1]

A. OVERVIEW OF THE CASE REGARDING OBVIOUSNESS.

What separates this case from the typical case, and certainly from the risperidone and olanzapine cases, is the amount of information in the prior art about Otsuka's own work that led

[1] As explained in Defendants' Opposition to Otsuka's Motion to Strike New Arguments Raised for the First Time in Defendants' Proposed Findings of Fact and Conclusions of Law, Defendants have raised no new obviousness arguments after trial.

to aripiprazole. Much of Otsuka's development of aripiprazole was made known to the world by means of its prior art patents and scientific literature. That constitutes the base against which the patentability of aripiprazole must be judged. In *KSR International Co. v. Teleflex, Inc.*, 550 U.S. 398, 427 (2007), the Supreme Court said, "[A]dvances, once part of our shared knowledge, define a new threshold from which innovation starts once more." Learned Hand in *Condenser Corp. v. Micamold Radio Corp.*, 145 F.2d 878, 879 (2d Cir. 1944), likewise said, "[W]hatever the benefit which the inventor who takes a last step has in fact conferred, he will be credited only with the ingenuity necessary to pass beyond the earlier" steps that are part of the prior art citable against his invention. In other words, it is this Court's task to decide whether that last increment of work that went from the prior art carbostyrils to aripiprazole is worthy of patent protection.

1. *The Prior Art Taught the Use of Carbostyrils to Treat Schizophrenia.*

That carbostyrils would be useful as antischizophrenic drugs was not a new idea in 1988. Otsuka's '416 patent (DTX 6, Col. 3:16) said so. Otsuka's SE '945 Swedish published patent application (DTX 1159-T at 5, ¶ 1) said so. Otsuka's '932 patent (DTX 20, Col. 2:62) said so. Otsuka contends that treating schizophrenia is just one use in a long list of possible uses mentioned in those patents, but the prior art says more than that.

The Nakagawa Declaration tested nine carbostyril compounds from the '416 patent and found that each had "excellent" activity in the mouse jumping test. (DTX 214 at 14.) Professor Marshall explained at length how the mouse jumping test correlates to antipsychotic potential. (Marshall 2189:23-2194:9 (explaining DTX 375 (Lal) and DTX 509 (Creese).) This ought to have been a nonissue in light of Otsuka's own prior statements concerning the test.

In the prosecution history of Otsuka's prior art '932 patent, Otsuka's attorney, Thomas Irving of the Finnegan firm, told the Patent Office (PTO) that the mouse jumping test is "a test method for determining whether a compound will have antischizophrenic activity." (DTX 471 at

4.) Now, in this litigation, Otsuka disparages the mouse jumping test and says that it is not really an indicator of antischizophrenic potential. Usually it is the accused infringer that is accused of hindsight, but here Otsuka's *volte-face* is its own form of hindsight revisionism.

Then there is the admission by Otsuka's own chemistry expert Professor Nichols that mouse jumping was used by Otsuka to test for antischizophrenic effectiveness. At first Prof. Nichols professed not to know for what the mouse jumping was useful, but under the Court's persistent questioning he finally conceded to its use as a test for antipsychotic potential. (Nichols 1642:5-9.)

The Nakagawa Declaration says that all nine of the carbostyrils it tested did "excellent" in the mouse jumping test, and the evidence establishes that this test is an indication of antischizophrenic usefulness. Accordingly, the prior art Nakagawa Declaration constitutes *empirical* evidence that certain carbostyrils would have been expected to treat schizophrenia. Defendants' case is not built on theory. It is built on test results—*empirical* data.

The only "theory" used is the dopamine hypothesis of schizophrenia. That was generally accepted in 1988 and is still generally accepted now. Otsuka's own expert, Dr. Roth, testified (Roth 1127:19-25) that this principle, that you treat schizophrenia by blocking dopamine, was the guide for developing antischizophrenic drugs. Dr. Oshiro also testified unequivocally that it was believed in the late 1980s that schizophrenia was caused by excessive dopaminergic activity. (Oshiro 1808:11-19.) Applying the dopamine hypothesis to the test results in the Nakagawa Declaration gave the person having ordinary skill in the art ("PHOSITA") an empirical basis for expecting carbostyrils to be useful for the treatment of schizophrenia.

There is more such empirical evidence in the prior art. For example, the Hiyama abstract (DTX 514) reports on multiple animal tests done on OPC-4139, which is one of the nine

carbostyril compounds in the Nakagawa Declaration. Hiyama says that OPC-4139 is "preclinically shown to have similar pharmacological actions to conventional neuroleptics." It also says that preclinical test "results suggest that OPC-4139 is potent in suppressing the dopaminergic activity."

Professor Marshall's testimony confirms Dr. Hiyama's statement that OPC-4139 is a neuroleptic compound. Antagonist action is the mark of a neuroleptic. (Marshall 364:23-365:3.) Dr. Marshall testified that the testing reported by Hiyama on OPC-4139 shows D_2 antagonist action in the anti-apomorphine climbing test.

> Q. "The compound inhibited apomorphine-induced climbing behavior of mice. While the compound did not antagonize apomorphine-induced stereotypy." If climbing behavior is stereotypical behavior, why didn't it antagonize the stereotypy behavior? It's the same compound, apomorphine?
>
> A. It is the same compound, and there could be many reasons for this. But one of the things that I learned early on in my career of doing behavioral tests in animals is an important principle, I believe, which is that -- the principle, as I would state it, is that the lack of an effect of a particular treatment cannot be construed as absence for the -- for the absence of a -- let me restate that, please.
>
> Q. Sure.
>
> A. I bolloxed that up.
>
> The absence of an effect of a particular treatment cannot be construed as evidence that that effect is absent. So in other words, bringing this back to the interpretation of experimental findings such as these, a positive behavioral response in one test simply has more weight for the neuropharmacologist investigator than a negative behavioral response.
>
> So a worker of ordinary skill looking at these data at the time would have considered that this drug did indeed have D_2 antagonist action, the OPC-4139 had D_2 antagonist action, and would have searched for an explanation of why the compound was not effective in the Apomorphine-Induced Stereotypy Test.
>
> And although I can't say for certain why that is, it's important to note that in the testing of these compounds, there are always false negative results. There are -- that just happens in animal testing models.

> And in this case it may be that species difference played a role. It may have contributed to this difference in outcome. The apomorphine-induced climbing behavior, as noted here, was performed in mice, and it appears that the apomorphine-induced stereotypy was characterized – was conducted in rats.

(Marshall 2187:4-2188:17.)

Otsuka relies on Dr. Roth's testimony about Hiyama, but Dr. Roth does not discuss the climbing test result or attempt to resolve the possible conflict between the climbing test result reported by Hiyama and the stereotypy test reported by Hiyama. The record does, however, have an explanation that fits with Dr. Marshall's suggestion. Dr. Oshiro testified that there is a species effect when carbostyril compounds are tested in rats. In particular, the compounds are rapidly metabolized. (Oshiro 1751:1-4 ("Q. Why did you request a test using mice? A. I believe that the carbostyril derivatives, including the compound OPC-4392, was -- were metabolized quickly if we used rat.").) Therefore, OPC-4139, a carbostyril derivative, would have been rapidly metabolized in the anti-apomorphine stereotypy test in rats reported by Dr. Hiyama, causing the test to come out negative because OPC-4139 would not have had a chance to show its antagonist action.

The animal testing reported in the Nakagawa Declaration and the Hiyama Abstract take us much further than the disclosure in the '416 patent. They provide *empirical* evidence of the antischizophrenic potential of carbostyrils.

The prior art does not stop there. There is also OPC-4392. The meaning of the clinical results for OPC-4392 was hotly contested. However, two prior art references came out with several noteworthy findings regarding antischizophrenics that would have caught the attention of a PHOSITA. The primary prior art reference regarding the clinical results for OPC-4392 is the 1987 Murasaki article (DTX 388-T). Another important one is the 1988 Gerbaldo abstract (DTX 990). Both Murasaki '87 and Gerbaldo report improvement in the negative symptoms of

schizophrenia. That was a very noteworthy piece of news. "Typical" antischizophrenic agents did not treat the negative symptoms. (Castagnoli 626:29-627:5; Roth 1144:6-11.) Moreover, there were no animal tests available that correlated to this activity. (Press 152:9-153:10.) So the PHOSITA would have paid a great deal of attention to this report of a compound that alleviates the negative symptoms.

Both Murasaki '87 and Gerbaldo report an absence of extrapyramidal symptoms ("EPS") with OPC-4392. That was noteworthy as well because "typical" antischizophrenic drugs cause EPS. (Press 153:22-154:19, 208:10-14; Castagnoli 803:19-804:3; Roth 1182:23-1183:11; Nichols 1531:21-1532:20.) It was only with the advent of clozapine that science even thought that an antischizophrenic drug could be uncoupled from EPS side effects. (Press 195:5-20; Roth 1128:23-1129:5; Nichols 1531:21-1532:20.)

Murasaki '87 also reported that OPC-4392 lowered prolactin levels. That, too, was noteworthy because prior art antischizophrenics had the adverse side effect of raising prolactin levels. (Castagnoli 622:12-19; Roth 1148:16-1149:5.)

Murasaki '87 also reported some nausea and vomiting, but this did not prevent OPC-4392 from being administered to humans, nor disqualify it from being a candidate for further testing. For example, Murasaki '87 characterizes the compound as an antipsychotic drug, and anticipates OPC-4392 being used in the treatment of the chronic stage of schizophrenia. (DTX 388-T at 1517 ("This is a totally new compound that is an anti-psychotic drug being developed in our country" and "there is anticipation for treatment of the chronic phase of schizophrenia").) Thus, Murasaki himself was of the view that the nausea and vomiting reported in the Phase II trials could be dealt with. As explained by Prof. Castagnoli (Castagnoli 627:24-628:15), Murasaki '87 suggests that nausea and vomiting can be handled by adjusting dosage. In addition, Dr. Press

testified (Press 155:6-13) that issues of nausea and vomiting could be addressed by adjusting the formulation.

So far, we have discussed how the clinical testing of OPC-4392 showed it to have effectiveness on negative symptoms and a good side-effect profile. What then about "positive" symptoms? Murasaki '87 reports that OPC-4392 was "not strong." The parties dispute what that means. Prof. Castagnoli (Castagnoli 625:13-626:1) testified that "not strong" means *some* activity. Otsuka, on the other hand, says it means no activity at all. Who is right? Look at the language itself. If *no* activity had been observed, one would expect Murasaki to report that in so many words. Instead, he says "not strong," which indicates weak activity, not no activity. In fact, at the time, as shown by Otsuka's own internal documents, Otsuka came to the same conclusion. (PTX 34-T at OPC0768534-T ("weak on the positive symptoms"); DTX 59-T at OPC0717008 ("Positive Symptoms – weak").) In fact, although none of Otsuka's witnesses mentioned it, Otsuka put OPC-4392 into Phase III trials based on the Phase II results. While this is *not* prior art, it is a contemporaneous evaluation that belies Otsuka's litigation-induced position. What we have here is another instance of hindsight revision by Otsuka.

Imagine for a moment that Otsuka's litigation-induced position were right—that is, that OPC-4392 was such a failure in clinical testing in humans that no one would ever again try a carbostyril as a candidate antischizophrenic drug. In that event, the '528 patent-in-suit would be invalid under Sections 101 and 112. That conclusion follows from the undisputed fact that only human testing really tests antischizophrenic effect with 100% certainty, whereas animal testing can give false positives because it only models treating schizophrenia rather than actually treating schizophrenia. Per Otsuka's view, the human testing on OPC-4392 spoiled the outlook for all carbostyrils as antischizophrenics. There is not enough evidence in the '528 patent to

change that assumed conclusion. The '528 patent has *no human data* and only *one* animal test that corresponds to antischizophrenic potential. That *one* animal test is known to sometimes yield false positives. (Marshall 2188:22-2189:3.) It would not convince a reader to abandon Otsuka's notion that the *human* testing of OPC-4392 forecloses carbostyrils as antischizophrenics. The '528 patent, however, is not invalid under §§ 101 and 112, because the proper view of the evidence is that the human testing on OPC-4392 in fact, and as a matter of fact, indicates that carbostyrils are candidates for antischizophrenic drugs.

So, in summary, Otsuka's prior art patent documents and scientific publications disclose that carbostyrils are useful as antischizophrenics. In addition, they provide *empirical* evidence that carbostyrils in fact have that potential usefulness.

2. *Aripiprazole Is Not Patentably Different from the Closest Prior Art Carbostyrils.*

Given that carbostyrils are in the prior art and that the prior art suggests that they can be used to treat schizophrenia, the question before the Court is whether aripiprazole is different enough from the prior art carbostyrils to be deserving of patent protection. That takes us to the question of obviousness under § 103. One way to look at this case is that it presents the problem of what is sometimes called a "selection invention." *In re Krazinski*, 347 F.2d 656, 661 (C.C.P.A. 1965). Aripiprazole is a member of the genus of carbostyrils in the prior art. Indeed, aripiprazole is itself covered by the claims of the prior art '416 patent.[2] How do the courts go about deciding whether a compound that is selected from a prior art genus is itself eligible for another patent protection? What the courts do is compare the selected compound to the prior art

[2] Aripiprazole is not only *covered* by the claims of the '416 patent but, by listing the '416 patent in the Orange Book, Otsuka indicated to the public that the '416 patent actually *claims* aripiprazole. (D.I. 328 at 9, ¶ 28 ("Otsuka had also listed U.S. Patent No. 4,734,416 ('the '416 patent') in the Orange Book for [aripiprazole]."); 21 U.S.C. § 355(c)(2) (requiring for listing in the Orange Book "any patent which claims the drug").) Otsuka, therefore, has claimed aripiprazole in the '416 patent and has claimed aripiprazole in the '528 patent.

genus to see if it is unexpectedly superior enough to deserve its own patent. *E.g.*, *In re Susi*, 440 F.2d 442, 445-46 (C.C.P.A. 1971); *Krazinski*, 347 F.2d at 661; *In re Lemin*, 332 F.2d 839, 841 (C.C.P.A. 1964). Of course, it is impossible to compare the selected compound to every member of the prior art genus. So, instead, it is compared to the prior art compound that is structurally closest because the compound closest in structure is more likely than the others to share the allegedly special properties of the selected compound.

That very sort of comparison is what happened during reexamination. After unsuccessfully trying to avoid rejections based on the '416 patent and other prior art, Otsuka presented the PTO with the Hirose Declaration. (DTX 121 at 01365-01400.) It compared aripiprazole to the prior art 2,3-dichloro propoxy compound. Otsuka and the examiner had agreed that that was the closest prior art. Aripiprazole and the 2,3-dichloro propoxy compound have but one difference—the length of the linker. Aripiprazole has a 4-link "butoxy" linker whereas the 2,3-dichloro propoxy compound has 3 links. Otsuka told the examiner that this difference in the linker length made aripiprazole "unexpectedly" superior to the 2,3-dichloro propoxy compound. The examiner was convinced by Otsuka. It is the sole reason mentioned by her when she allowed the claims. (DTX 121 at 01412.)

Although Otsuka itself invited the examiner to compare aripiprazole to the structurally similar 2,3-dichloro propoxy homolog during reexamination, Otsuka now criticizes Defendants' analysis as out of step with the Federal Circuit's mode of obviousness analysis expressed in *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 2010 U.S. App. LEXIS 18820 (Fed. Cir. Sept. 9, 2010). However, *Daiichi* was not a genus/species selection invention case—the patentee there had not previously patented the genus covering the subsequently claimed species compound. The question never came up whether the claimed species had a "special significance," *Lemin*,

332 F.2d at 841, over the prior art genus that included the claimed species. Instead, in *Daiichi* the accused infringer could only start the obviousness analysis with a structurally close prior art compound that had no such relationship to the claimed compound.

Here, by contrast, there already were teachings that the prior art genus that included aripiprazole and its structurally similar propoxy homolog would be expected to exhibit antischizophrenic activity. Indeed, that was a premise of the '416 patent and its Swedish counterparts, each of which specifically exemplified the 2,3-dichloro propoxy homolog of aripiprazole and used this antischizophrenic activity as one of the justifications for the genus that was claimed therein. (DTX 6, Col. 3:13-23 ("Therefore, compounds of the present invention are useful for central nervous controlling agents such as central muscle relaxing agents, sleep-inducing agents, pre-operative drugs, **antischizophrenia agents**, sedatives, antianxiety drugs, anti-manic depressive psychosis agents, antipyretic agents, analgetic agents and depressors, without showing side-effects such as the feeling of thirst, constipation, tachycordia [sic], **parkinsonism,** and/or **delayed dyscinesia [sic]** which exist with conventional central nervous controlling agents." (emphasis added).) Notably the side effects listed such as delayed dyskinesia are side effects associated with antipsychotic drugs. (*Id.*; *see also* DTX 248-T (DE '105) at 12 (discussing similar side effects including the avoidance of delayed dyskinesia); Roth 1144:12-1145:14 (discussing tardive dyskinesia and related side effects of antipsychotic drugs).)

As Dr. Press testified, many of the animal models discussed in the specification of the '416 patent and its counterparts are used to predict antischizophrenic activity, including tests for apomorphine vomiting inhibitory action, the spontaneous movement of rats, antimethamphetamine action, and methamphetamine group toxicity. (DTX 6, Col. 3:3-14 ("Furthermore, as to the central nervous controlling activities, the present compounds have

various pharmacological activities such as muscle relaxing action, apomorphine-vomiting inhibitory action, ptosis action, hypothermy action, spontaneous movement controlling action, hypermotion controlling action of rats, anti-methanphetamine [sic] action, methanphetamine [sic] group toxicities lowering action, analgetic action and anti-noradrenaline action but they have only weak activities in anticholine action, cardio-inhibitory action and catalepsy inducing action."); Press 121:6-123:3; 225:1-228:3.) Dr. Press used and interpreted the results of these animal models during his own research on antischizophrenic drugs. (Press 122:23-123:3.) Dr. Press concluded that these tests were *actually carried out* because inventors understand that they must be honest with the U.S Patent and Trademark Office. (Press 226:15-23.) The results of many of these tests are found in Otsuka internal documents and Otsuka publications in evidence. (DTX 208, 208-T at OPC0616307-09 (showing that 4000-series carbostyrils including those in the Nakagawa Declaration all tested for inhibition of locomotor activity, inhibition of fighting, inhibition of vomiting, inhibition of locomotor and group toxicity effects of methamphetamine, reduction in body temperature, and even halothane anesthesia); DTX 514 at 380.) The '416 patent also provides actual test data in Tables II and III for the halothane anesthesia test. Otsuka used the halothane anesthesia test to predict whether compounds would have antischizophrenic activity. (Oshiro 1846:9-19; 1849:24-1852:8; DTX 208, 208-T.)

Although not recognized at trial by Dr. Roth as a test for dopamine D_2 antagonism or antipsychotic potential (Roth 1214:23-1215:9), the literature he cited shows that apomorphine-induced emesis (vomiting) in dogs is yet another test used to demonstrate dopamine D_2-receptor antagonism. PTX 305 by Janssen et al. (1988) was characterized by Roth as "a landmark paper" describing the pharmacology of risperidone. (Roth 1179:23.) At page 686, second column, of PTX 305 is the heading "Tests Related to Dopamine D_2-Antagonism" and only one dog test is

listed: "APO antagonism in dogs" where "[c]omplete absence of "EME" (emesis, see abbreviations on p. 685), in apomorphine-treated dogs was considered to reveal apomorphine antagonism. The abstract of that paper says that this study in "dogs reveals potent dopamine-D_2 antagonism." (*See also* PTX 305 at 692 (legend to Fig. 3 naming inhibition of apomorphine-induced emesis in dogs as a test related to dopamine D_2 antagonism).)

That inhibition of apomorphine-induced emesis in dogs was considered a useful test for antipsychotic potential is further supported by literature cited by Otsuka's medicinal chemistry expert, Dr. Nichols. PTX 436, also by Janssen (1970) at OPC0808378 states that "The most effective antipsychotic agents known are neuroleptics that are specific and long-acting inhibitors of induced stereotypies and emesis (amphetamine, apomorphine)." Defendants' pharmacology expert Dr. Marshall also cited literature using the apomorphine-induced emesis test as evidence of dopamine D_2 antagonism. (DTX 509 (Creese et al. (1976) at Table 1, 4th column, and discussion in the middle column of p. 482).)

Accordingly, Otsuka should be estopped from arguing that the representations made in the specifications of Otsuka's earlier patents to support broad genus claims do not also raise an expectation that compounds covered by that genus would have the same sorts of antischizophrenic activities touted in those specifications. Furthermore, as already discussed above, additional prior art provides *empirical* evidence that carbostyrils similar in structure to aripiprazole should be useful in the treatment of schizophrenia.

The PTO record is unequivocal that the reason for allowing the aripiprazole claims in the reexamination was the allegedly "unexpected" superiority of aripiprazole. (DTX 121 at 01412.) The empirical evidence, however, demonstrates that aripiprazole is not patentably superior to the 2,3-dichloro propoxy compound. In fact, the 2,3-dichloro propoxy compound met Otsuka's

criteria for development and commercialization as an antischizophrenic agent. Dr. Oshiro testified that he was looking to develop a compound that had better results than chlorpromazine in the anti-apomorphine stereotypy test. (Oshiro 1813:18-22.) The 2,3-dichloro propoxy compound was more active than chlorpromazine in the anti-apomorphine stereotypy test, with an ED_{50} value of 2.5 as compared to 3 for chlorpromazine. (Oshiro 1821:21-23; DTX 59-T at OPC0717014; Oshiro 1813:18-1814:7; PTX 35-T at OPC0768541.)

The reason that Otsuka did not advance the 2,3-dichloro propoxy was that Otsuka did not believe it could patent it. In an e-mail to Dr. Hirose, Dr. Oshiro explained that the "effective period on a patent for an OPC-4392 analogous compound [*i.e.*, a compound such as the 2,3-dichloro propoxy] is insufficient." (DTX 88 at OPC0726855.) Dr. Oshiro explained in a 2006 presentation that when he was looking to develop a post OPC-4392 compound, "[b]ecause a number of similar compounds had already been synthesized, the first hurdle to clear was to find a compound that could be patented." (DTX 268-T at OPC0771184.) In fact, Dr. Oshiro testified that it was a policy at Otsuka that a compound could not be commercially developed unless it could be patented. (Oshiro 1827:11-16.)

The Hirose Declaration reports *no difference at all* between the two compounds in the anti-epinephrine lethality test. The only difference in Dr. Hirose's test results between aripiprazole and the 2,3-dichloro propoxy compound is in the anti-apomorphine stereotypy test. Dr. Hirose's declaration purports to show that aripiprazole is 23 times more potent in that test. Otsuka had prior test results, however, showing only a 6-times difference. (Oshiro 1844:8-1845:9; PTX 37-T at OPC0768548T; DTX 59-T.) No Otsuka witness ever explained the discrepancy between the 6-times result in Otsuka's internal tests and the 23-times result submitted to the PTO.

It is undisputed that the tests yielding the 23-times number were run for the very purpose of convincing the PTO of patentability—and that the testers knew that was the purpose of that testing. On the other hand, the tests yielding the 6-times number were run earlier, for genuine scientific reasons, and not to support legal arguments. As between the two sets of data, the earlier 6-times number is more credible than the later 23-times number generated for the sole purpose of convincing the PTO of patentability. We know that co-inventor Dr. Oshiro did not regard a 6-times increase to be a noteworthy increase. (Oshiro 1772:12-1773:3; 1843:21-1845:9.) If a co-inventor does not regard six times as considerable enough to be noteworthy, then neither should this Court.

Otsuka's lawyers now try to argue that this 6-times versus 23-times issue took them by surprise. That is nonsense. The contemporaneous 1987 data showing the mere 6-times difference in stereotypy potency is contained in a document that Otsuka produced to Defendants in this litigation and that Otsuka's counsel offered into evidence at trial before Dr. Oshiro even took the stand. (DTX 59-T; Goolkasian 548:21-553:1 (on cross-examination).) Otsuka then featured the argument that its 2005 stereotypy testing showed that aripiprazole was 23 times more potent than prior art propoxy dichloro homolog with several of its witnesses—going so far as to place a star around the 23x number. (PD-310.) Surely Defendants were entitled to challenge this argument based on Otsuka's own contemporaneous data. Indeed, the real question here is why Otsuka did not bother to tell the PTO or the Court that it had data from 1987—the time of its alleged "discovery" of aripiprazole that contradicted its 23-times better data and demonstrated that when Otsuka was testing the compounds outside the context of trying to overcome a final rejection on reexamination, aripiprazole was only six times more potent.

Even if we assume for the sake of argument that relevant "superiority" is shown by 6-times more potency—or for that matter 23-times more potency—in the anti-apomorphine stereotypy test, there is still the question whether such an improvement is "unexpected" from substituting a butoxy 4-linked linker for a propoxy 3-linked linker. The evidence demonstrates that an improvement was to be expected, not unexpected.

Foremost, there is the Nakagawa Declaration (DTX 214). It is undisputed that the unsubstituted butoxy compound is more potent in the mouse jumping test than the unsubstituted propoxy compound. That alone is enough to refute the notion that an improvement in potency is not to be expected in switching to a butoxy linker.

The Nakagawa Declaration is not alone. There is also the Wise Poster (DTX 398). Otsuka resists the Wise Poster on multiple grounds. First, Otsuka says the Wise Poster is not prior art, but the Federal Circuit's decisions in *In re Klopfenstein*, 380 F.3d 1345 (Fed. Cir. 2004), and *Massachusetts Institute of Technology v. AB Fortia*, 774 F.2d 1104 (Fed. Cir. 1985), establish that the Wise Poster is a "printed publication" under 35 U.S.C. § 102(b). Otsuka responds that Dr. Wise's testimony about the poster is not "corroborated." No corroboration requirement was mentioned for the posters in the *Klopfenstein* or *MIT* cases. Corroboration comes up in other contexts, typically where an alleged prior inventor's oral testimony is being used to show a prior invention or a prior public use. Oral testimony requires corroboration because of the need to confirm that the technical details were as the witness remembers. There is no need for that with a printed publication because the document itself reports those details. To the extent that corroboration is required for the oral testimony that authenticates the poster, it is provided by, among other things, Otsuka's own Haruki Memo (DTX 274-T) that reports on Parke-Davis's disclosure of its coumarin work at the 1987 Society for Neuroscience conference

in New Orleans. The idea behind the corroboration requirement is to make sure that the witness is telling the truth. There is absolutely no reason to believe that Dr. Wise was not accurately testifying that this poster was displayed at the 1987 conference.

Otsuka also attacks the Wise Poster on the ground that it deals with coumarins rather than carbostyrils. The evidence establishes that coumarins and carbostyrils are closely related. Professor Castagnoli explained (Castagnoli 646:3-647:24) that they differ only in the substitution of an oxygen for the nitrogen/hydrogen in the carbostyril ring, that they are "isosters"—meaning that they have similar electronic configurations, that they have nearly identical shapes, and that they are expected to have similar chemical, spectral, and reactive properties. He also explained that the Wise Poster is directed at the same target disease, namely, schizophrenia. (Castagnoli 652:1-20.)

This close relationship between coumarins and carbostyrils was repeatedly recognized by Otsuka before it got involved in this litigation. During the interference that involved the application leading to the '416 patent, Otsuka's expert told the PTO that coumarins and carbostyrils are closely related. (Bodor Dep. 41:7-9.)[3] In addition, there is Otsuka's own Haruki Memo (DTX 274-T) that notes the similarity in chemical structure and pharmacological properties of coumarins and carbostyrils. (DTX 274-T at OPC0730595 (also listing inventor Oshiro as a recipient of the memo), OPC0730604, Col. 2 (explaining that coumarins have utility treating psychoses such as schizophrenia).)

Further, Otsuka itself investigated coumarins because any researcher would want to know about the coumarins.

[3] Otsuka objects to Dr. Bodor's testimony as hearsay, but it is not hearsay as to Otsuka because Dr. Bodor was Otsuka's own expert in the interference. Fed. R. Evid. 801(d)(2)(A)-(D).

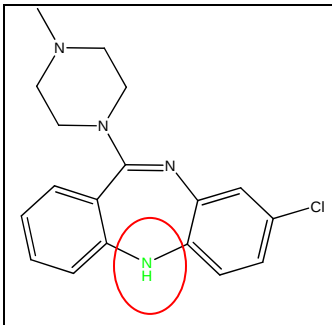
> Q. What was your motivation for selecting coumarin as one of the possible alternatives?
>
> A. You can investigate numerous compounds if you investigated different types, different compounds rather than investigating the same group of compounds, and so rather than investigating one group you should investigate two groups, you may be able to find something with efficacy. In addition, these that are described here all have a hetero ring attached to the phenyl ring. I was looking into the difference between N and O, what happens if one is replaced with the other. **I think any researcher would be interested in knowing that.**

(Banno Dep. 87:9-23 (emphasis added).) Also, the coumarin derivatives were active in the jumping test and further explored by Otsuka. This undercuts the testimony by Otsuka's witnesses that coumarins would not have been considered close analogs of carbostyrils.

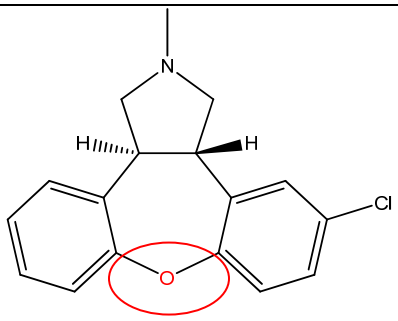
> Q. Do you recall whether that one small success in coumarin led to further research into the coumarin compounds?
>
> A. Since it was found effective in suppressing the jumping activities, meaning [OPC-]4396 having the effect, I believe or we must have made more coumarin derivatives and that can be said from looking at this, as well.

(Banno Dep. 96:18-25.)

Otsuka's attacks on the similarity of the coumarins and carbostyrils is in sharp contrast to Dr. Nichols' testimony concerning clozapine and its analogs. For example, in comparing clozapine to asenapine, a clozapine isostere that differs from clozapine by, *inter alia*, substituting a nitrogen on one of clozapine's rings for an oxygen, Dr. Nichols testified that these compounds were in fact similar:



Clozapine



Asenapine

(PD-614.)

> And although it looks somewhat different, to a medicinal chemist they would identify this tricyclic central core as being similar to clozapine, in my opinion.

(Nichols 1600:22-24.)

As coumarins have oxygens where the carbostyril core ring has nitrogen, asenapine has an oxygen where the clozapine core ring system has a nitrogen. Unlike coumarins and carbostyrils, asenapine has other major structural differences from clozapine. There is no principled basis to regard the carbostyrils and coumarins isosteres as nothing alike, and yet at the same time regard the clozapine and asenapine isosteres as "similar." Accordingly, Otsuka's attempt to distance carbostyrils from coumarins is yet another instance of Otsuka's litigation-induced hindsight revision of its own history.

The Wise Poster did a structure-activity relationship study of the effect of linker length. It found that the butoxy linker was more potent than the propoxy linker. In fact, the Wise Poster's SAR study on linker length shows that the 4-linked butoxy is better than not just the 3-linked propoxy but also better than linkers with 2 or 5 links. Thus, the butoxy linker is at the top of the parabolic curve that one expects for a homologous series. (Castagnoli 733:21-735:20.)

Homologation is the name given to changing a molecule by adding one more methylene (CH_2) group, which is what happens when one goes from a propoxy to a butoxy linker. Such is the "simplest chemical change that can be made." (DTX 1012 at 306 (Ing).) Indeed, this homologation strategy is "as old as organic chemistry." (DTX 621 at 337 (BURGER'S MEDICINAL CHEMISTRY).) Because homologation was such a common strategy, it was obvious to try the butoxy linker. But the evidence goes well beyond mere obvious to try. The test results

in the Nakagawa Declaration and the Wise Poster show that the butoxy linker is expected to produce the most potent compound.

Thus, what Otsuka told the PTO was "unexpected" was *not* really "unexpected." Test results in the prior art taught improvement was to be *expected* in going from a propoxy to a butoxy. Without unexpected results, aripiprazole is unpatentable over the prior art genus of carbostyrils.

That is one way to compare aripiprazole to the prior art genus of carbostyrils. There are other representatives of that prior art genus to which aripiprazole can be compared. The unsubstituted butoxy compound is discussed above at greater length in the discussion of obviousness-type double patenting. As explained above, the prior art Nakagawa Declaration and Wise Poster together present an overwhelming case that the butoxy linker is the linker length that one ought to use. The unsubstituted butoxy provides the ideal starting point for developing compounds that have that type of linker. As Dr. Press put it (Press 166:9), the unsubstituted butoxy is the "perfect platform" for exploring such compounds. The prior art suggests putting chlorines at the 2 and 3 positions of the unsubstituted butoxy. In particular, this is suggested by the empirical teachings of the test results in the Nakagawa Declaration. Aripiprazole would be the result of putting chlorine at those positions, thereby demonstrating again the obviousness of aripiprazole.

OPC-4392 is yet another excellent representative of the prior art genus of carbostyrils. OPC-4392 stands out because it was tested in humans. As already discussed, OPC-4392 nearly achieves all the goals on the wish list for an antischizophrenic drug. It treats negative symptoms. It has a good side-effect profile. In particular, it does not have the EPS problems of a typical

antischizophrenic. Its shortcoming is that it is "not strong" in treating positive symptoms. The prior art suggests what to do about that.

As already explained, the Nakagawa Declaration and the Wise Poster strongly suggest stretching the linker by one link to make it a butoxy linker. Likewise, the Nakagawa Declaration and the Wise Poster strongly suggest substituting chlorines for the methyl substituents on the phenyl ring. The Wise Poster has quite a strong teaching on this point. In 3 out of 3 tests the compound with chlorine at the 3 position does better than the compound with methyl at this position. (Castagnoli 738:2-739:22.) This is a strong suggestion to substitute chlorine for methyl in OPC-4392. Some of the prior art compounds are single bonded **di**hydros. All nine of the Nakagawa Declaration compounds are such. Some of the prior art compounds are double bonded **de**hydros. OPC-4392 and all the Wise Poster compounds are such. There are no head-to-head studies of dihydro vs. dehydro, and so there is no empirical basis for picking one or the other. So the PHOSITA would do both. (Castagnoli 662:5-663:11; 667:4-18.) In fact, that approach of making both single and double bonded is suggested by the '416 patent that does about 250 pairs of single and double bonded carbostyrils. (Castagnoli 662:663:11; 665:4-666:6.)

As Prof. Castagnoli explained (Castagnoli 797:15-801:13), if one makes these changes—that is, use a butoxy linker, substitute chlorine for methyl at one or both positions on the phenyl ring, and make both single and double bonded carbostyrils, one ends up with a small group of 8 compounds. Each is obvious. Aripiprazole is a member of that group of obvious compounds. The law does not require Defendants to prove that aripiprazole is the only, or even the best, choice. *In re Fulton*, 391 F.3d 1195, 1200, 1201-02 (Fed. Cir. 2004); *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989); *Carter-Wallace, Inc. v. Otte*, 474 F.2d 529, 543

(2d Cir. 1972). Indeed, it only makes sense that there are many obvious compounds. It is the unobvious compound that would be unique. The obvious ones would just be part of the crowd.

As Prof. Castagnoli explained (Castagnoli 677:4-23; 801:14-25; 803:9-804:3; 816:16-22), the PHOSITA would expect these 8 compounds to have the good features of OPC-4392—namely, good on negative symptoms and a good side-effects profile. The PHOSITA would also expect them to have strong antipsychotic potency. That, after all, is why the changes to linker length and substitution of chlorine were made.

The PHOSITA would have had those expectations, but of course these compounds would have to had been tested. But the law does not require foreknowledge of the results. It requires only reasonable expectations. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007); *Merck v. Biocraft*, 874 F.2d at 809; *In re O'Farrell*, 853 F.2d 894, 903-04 (Fed. Cir. 1988); *In re Longi*, 759 F.2d 887, 897 (Fed. Cir. 1985).

Otsuka argues that the prior art suggests other modifications, such as switching the linker attachment position to the 5 position instead of the 7 position. Prof. Castagnoli (Castagnoli 793:19-794:20) and Dr. Press (Press 159:8-164:10) explained why that would not be done, at least not as part of the first set of new compounds. But even if that option were added, the total number of obvious compounds would only go from 8 to 16. That is far fewer than the 1,200 in the *Merck* case. 874 F.2d at 807.

Otsuka's witnesses provide only conclusory testimony with no support for their argument that one would go with the strongest compound. They also do not give supported reasons why the 7-linked compounds would be excluded. Both Drs. Press and Castagnoli gave opinions that going from 7-linked compounds to 5-linked compounds would be a substantial change that a person of ordinary skill in the art would not prefer to make. Dr. Press because changes near the

core are undesirable (Press 163:4-16), and Dr. Castagnoli because small changes were preferred (Castagnoli 793:19-794:20; 841:1-5). But unlike Otsuka's experts, Drs. Press and Castagnoli have documentary support for favoring the study of 7-linked compounds like OPC-4392, but not excluding, the 5-position compounds.

> Thus, we are confronted with a paradox: we select compounds for testing because they resemble a 'lead' structure, and also because they differ significantly from the 'lead,' or from any other compound known to be active in the test system. In this position *one usually gives priority to close structural analogs, rather than to untested novel structures*.

(DTX 621 at 335 (Paul N. Craig, *Analog Drug Design* in BURGER'S MEDICINAL CHEMISTRY, 331, 335 (4th ed. 1980) (emphasis added).)

Summarizing what we have discussed so far, we see that aripiprazole results from optimizing according to prior art teachings each of three different representatives of the prior art genus of carbostyrils. Any one of these would be a sufficient basis for holding aripiprazole obvious. Taken together, they make an overwhelming case for unpatentability over the prior art genus of carbostyrils.

3. *Otsuka's "Objective Indicia" Evidence Is Weak.*

As one would expect in such circumstances, Otsuka offered evidence purporting to support unobviousness based on the so-called objective indicia of nonobviousness (a/k/a secondary considerations). Most of these secondary considerations depend from their relevance on the same inferential logic—namely, that if aripiprazole were really obvious, then others would have tried to make and bring it to market, too, but since Otsuka was the only one to do that, then the inference is that others must have tried and failed, thereby showing that aripiprazole is not obvious after all. Such is the inferential logic of relying on the failure of others to meet a long-felt need. Such is also the inferential logic that justifies reliance on some other of the secondary considerations. *In re D'Ancicco*, 439 F.2d 1244, 1248 (C.C.P.A. 1971),

says that such is also the logic behind reliance on unexpected results. *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005), says that such is also the logic behind reliance on commercial success.

In this case, that inference cannot be drawn because of Otsuka's prior blocking patents. In other words, the failure of others to make aripiprazole is explained by Otsuka's already having gotten legal exclusivity covering carbostyrils and not by any technical hurdles. The courts have recognized how patents can discourage research by others in the claimed field. *Brenner v. Manson*, 383 U.S. 519, 534 (1966); *Princo Corp. v. ITC*, 616 F.3d 1318, 1350 (Fed. Cir. 2010) (Dyk, J., dissenting); *Aventis Pharma S.A. v. Hospira, Inc.*, Nos. 07-721, 08-496, 2010 WL 3842273, at *29 n.24 (D. Del. Sept. 27, 2010). The record also demonstrates that blocking patents really do discourage research in this field. For example, Dr. Press testified (Press 80:11-81:5, 190:8-20) about how Lederle abandoned its olanzapine project when confronted by Eli Lilly's superior patent position. Otsuka's expert Dr. Nichols testified (Nichols 1712:17-1714:10) that a pharmaceutical firm would likely *not* pursue a lead compound once it learned that it was covered by another firm's patent. Otsuka itself had a policy of not pursuing compounds that could not be patented by Otsuka. (Oshiro 1827:11-16.) Otsuka points to recent patents for improvements on aripiprazole (such as different crystal forms and salts of aripiprazole), but those patents postdate the approval of aripiprazole as a commercial drug and relate to getting ready to market aripiprazole once the patents expire. They do not tell us anything about how research on the basic drug would have proceeded years earlier.

In response to the problem of Otsuka's blocking patents, Otsuka argues that the case at bar is analogous to *Takeda Chemical Industries, Ltd. v. Mylan Labs., Inc.*, 417 F. Supp. 2d 341, 387 (S.D.N.Y. 2006), *aff'd*, 492 F.3d 1350 (Fed. Cir. 2007) (affirming obviousness), *later*

appeal, 549 F.3d 1381 (Fed. Cir. 2008) (affirming fee award). To begin with, the Federal Circuit did not even address the blocking patent issue in *Takeda*. 492 F.3d at 1363 (explaining that "we need not consider any objective indicia of nonobviousness"). There is, therefore, no basis for believing that the Federal Circuit intended to limit the reach of its opinion in *Merck* where the court held that reliance on commercial success was undermined by a blocking patent. 395 F.3d at 1377. Furthermore, the district court in *Takeda* was faced with a different set of facts. In *Takeda* there was evidence that someone had actually developed a compound from the "TZD" class of compounds to compete with the plaintiff's compound from the same "TZD" class. 417 F. Supp. 2d at 387 ("Takeda's competitors had every opportunity to develop new compounds that were improvements over the compounds Takeda disclosed."). In contrast, as Otsuka has been at pains to repeatedly point out, there has been no other carbostyril approved as an antischizophrenic.

Otsuka fails to address Dr. Press's testimony regarding why development of otherwise promising drugs does not happen when there are blocking patents. The testimony indicates that the reason that developmental work will not occur on patented compounds is that the drug company would be sued if it sold the drug, so it could not make money. Dr. Press, a man who had to make decisions about the direction of drug development at several companies (Press 81:9-82:16), testified that:

> But as a scientist, I always hate to admit this, but pharmaceutical companies do this because they hope to make a drug out of it to make money.
>
> If they have their scientific staff looking at a drug or drug candidate that's owned by somebody else, they're not expending their resources very well.
> And so people in another company that don't own the compound wouldn't pursue those compounds because they know they wouldn't have a benefit to their company at the end.

(Press 174:15-174:23.) Dr. Press further testified:

> And as a nonpatent lawyer, my medicinal chemistry experience already has experience with blocking patents.
>
> THE COURT: So you weren't rendering any legal opinion. You were simply just saying, this is what I lived through?
>
> THE WITNESS: That's correct. I lived through this. I had a research program shut down because of this.

(Press 313:10-313:17.) The '416 patent did not expire until March 2005. (Aripiprazole New Drug Application (DTX 35-A) at OPC0002045.) A competing drug company in 1988 would not have had an incentive to develop a drug it could not sell until the expiration of the '416 patent in March 2005. This directly undercuts the inference that is required to make commercial success probative of nonobviousness. *Merck*, 395 F.3d at 1376 ("Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art."). Just as in *Merck*, here, market forces could not bring aripiprazole to market sooner because competitors would have been sued for patent infringement under Otsuka's blocking '416 patent if they did.

> As our predecessor court explained in *In re Fielder, 471 F.2d 640, 644 (C.C.P.A. 1973)*, "these rationales, presumably approved by the [Supreme] Court, **tie commercial success and the like directly to the practical, financial source of impetus for research and development**." But that **chain of inferences fails on these facts**. Although commercial success might generally support a conclusion that Merck's claimed invention was non-obvious in relation to what came before in the marketplace, the question at bar is narrower. It is whether the claimed invention is non-obvious in relation to the ideas set forth in the Lunar News articles. Financial success is not significantly probative of that question in this case because others were **legally barred** from commercially testing the Lunar News ideas.

Id. at 1376-77 (emphasis added) .

Even if the Court were to assign some weight to Otsuka's commercial success evidence, the existence of multiple patents precludes the Court from determining how much weight to assign to that evidence. *McNeil-PPC, Inc. v. Perrigo Co.*, 516 F. Supp.2d 238, 254-55 (S.D.N.Y.

2007) (Plaintiff's product "is covered by at least three patents. . . . This makes it difficult to attribute whatever commercial success Pepcid Complete may enjoy to any one of the three patents."), *aff'd*, 274 Fed. App'x. 899, No. 07-2508, 2008 WL 1734560 (Fed. Cir. Apr. 14, 2008) . Both the prior art '416 patent and the '528 patent-in-suit were listed in the Orange Book as covering the antischizophrenic drug. (DTX 35-A; Nichols 1714:15-1716:3.) Other Otsuka patents cover other uses for aripiprazole. Otsuka is wrong when it argues that it was up to Defendants to apportion the commercial success between the prior art '416 patent and '528 patent. Similarly, Defendants were not required to establish the level of illegal sales of Abilify®. Rather, Otsuka, as the party with the burden of proving nexus and commercial success, had the burden of establishing the extent to which the alleged commercial success was attributed to the '528 patent as opposed to Otsuka's other patents. *See Fed. Pac. Elec. v. Wadsworth Elec.*, 221 F. Supp. 148, 152 (E.D. Pa. 1963) ("It should also be noted that the circuit breaker marketed by the plaintiff bears the notation of **27 patents** upon it and a court would have great difficulty in determining which patent or patents were responsible for its commercial success. It is true that there is no evidence that any of the above factors other than the patent in suit were responsible for the large sales achieved by the plaintiff. However, it is the plaintiff who is seeking to have the Court infer from the successful exploitation of the patent that its invention was unobvious, and **it is the plaintiff's burden to satisfy the Court that its success was, in fact, due to the merits of the patented invention rather than other factors**. If commercial success were material in this case, I would, therefore, have to conclude that the evidence of commercial success is insufficient to establish the patentability of the claims in suit.") (emphasis added).)

There are other problems with Otsuka's reliance on secondary considerations. Otsuka relies on after-the-fact developments concerning the properties of aripiprazole. For example,

there is Dr. Roth's heat map regarding activities of various receptors. There is also the approval of aripiprazole for uses other than the treating of schizophrenia. There are big fallacies with these arguments.

First, the existence of these additional properties, even if unexpected, do not negate the importance of the *expected* properties of aripiprazole. As already explained, the PHOSITA would have had certain reasonable expectations for the result of her optimization of prior art carbostyrils. She would have expected improved potency in treating positive symptoms, continued good potency in treating negative symptoms, and a continued good side-effect profile. Under the law, the expected and unexpected must be weighed together to ascertain the overall importance of this evidence in the obviousness analysis. *In re Eli Lilly & Co.*, 902 F.2d 943, 947-48 (Fed. Cir. 1990); *In re Nolan*, 553 F.2d 1261, 1267 (C.C.P.A. 1977); *Graceway Pharm., LLC v. Perrigo Co.*, No. 10-00937, 2010 WL 2400172, at *7 (D.N.J. June 10, 2010). For example, in *Nolan*, higher memory margin was expected and lower peak discharge current and higher luminous efficiency were *un*expected. The court weighed the two unexpected improvements against the one expected improvement and found that the expected improvement was more important because the object of the device was memory. 553 F.2d at 1267 ("The expected higher memory margin is of particular significance since it appears to be the most significant improvement for a memory device. Appellant has not shown that the unexpected lower peak discharge current and higher luminous efficiency have a significance equal to or greater than that of the expected higher memory margin and lower operating voltage.") The applicant's claims were, therefore, rejected for obviousness. *Id.* Likewise, here, the expected properties provided the PHOSITA with ample motivation to make aripiprazole for the purpose of treating schizophrenia. The existence of other unexpected properties does not dilute that

motivation. It would still have been obvious to make aripiprazole and use it to treat schizophrenia.

Another problem with Otsuka's reliance on Dr. Roth's heat map and its reliance on the other uses of aripiprazole is that there is *no evidence* that the relevant prior art carbostyrils do not also have these same properties. Even if these properties were "unexpected," they do not count in the obviousness analysis unless they constitute *actual differences* between aripiprazole and the closest prior art. That is the critical point made in *In re Hoch*, 428 F.2d 1341, 1343-44 (C.C.P.A. 1970), and *In re Wilder*, 563 F.3d 457, 460 (C.C.P.A. 1977), which were quoted at length at pages 130-131 of Defendants' Proposed Conclusions of Law, and simply ignored in Otsuka's papers. As the proponent of the objective indicia evidence, it was up to Otsuka to present evidence of *actual differences* between aripiprazole and the closest prior art. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007); *In re Freeman*, 474 F.2d 1318, 1324 (C.C.P.A. 1973); *In re Susi*, 440 F.2d 442, 446 (C.C.P.A. 1971). Otsuka did not even try to do that. Instead, Otsuka compared the properties of aripiprazole to other *non*carbostyril antischizophrenics, some of which were not even in the prior art. No attempt was made to establish a difference in properties between aripiprazole and the closest prior art carbostyril compounds. Comparing aripiprazole to other noncarbostyril compounds does not get you the relevant information. What Otsuka is required to do to present *relevant* evidence is compare aripiprzole to the closest carbostyril prior art, and Otsuka did not do that.

Otsuka argues that "copying" is a relevant objective indicium of nonobviousness. Where, as here, the alleged "copying" is the result of the structure of the Hatch-Waxman Act, and not the failure to overcome some technical hurdle, however, the inference of nonobviousness is very weak or nonexistent. *Purdue Pharma Prods. L.P. v. Par Pharm., Inc.*, Nos. 09-1553, 09-1592,

2010 WL 2203101, at *4 (Fed. Cir. June 3, 2010) (unpublished); *Santarus, Inc. v. Par Pharm., Inc.*, No. 07-551, 2010 WL 1506017, at *26 (D. Del. Apr. 14, 2010). Furthermore, case law establishes that to be probative of nonobviousness, alleged copying by the accused infringer must be accompanied by additional evidence, such as failed development efforts by the accused infringer, *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp*., 72 F.3d 1577, 1583 (Fed. Cir. 1996); or of other "more compelling objective indicia of other secondary considerations." *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1380 (Fed. Cir. 2000) (citing cases).

An inference of nonobviousness based on copying is especially inappropriate in the context of ANDA litigation where the generic manufacturer's behavior is governed and incentivized by the regulatory requirements of the Hatch-Waxman Act, not by a failure to overcome some technical hurdle in the art. What is interesting about the evidence in this case is the fact that several other atypical antischizophrenics were developed at about the same time as aripiprazole. That shows that the level of skill in the art was high enough to overcome whatever hurdles existed to developing an atypical antischizophrenic. That none of these others were carbostyrils is readily explainable by the blocking effect of Otsuka's prior patent portfolio. There is no basis for inferring that technical hurdles blocked that development.

These same reasons undermine Otsuka's attempt to rely on the alleged failure of others to meet a long-felt need. Otsuka's blocking patents and the barriers erected by the regulatory system restricted others from optimizing the prior art carbostyril compounds (as Otsuka did).

Another problem with Otsuka's reliance on the alleged failure of others is the short time between the availability of the most relevant prior art and the filing date of its patent application. *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966); *Carter-Wallace, Inc. v. Otte*, 474 F.2d 529,

546 (2d Cir. 1972). For example, the Nakagawa Declaration became public less than a year before Otsuka's filing date of the Japanese priority patent that is Otsuka's *de jure* invention date.

Finally, Otsuka makes much of the acclaim given to aripiprazole. In the circumstances of this case, these prizes do not support the conclusions of nonobviousness. In this case, much of Otsuka's own prior development work is part of the prior art that counts against patentability. There is no evidence that the awarding of these prizes made any attempt to sort out the last increment of work that led to aripiprazole. Indeed, why would they even attempt to do so? Thus, the analysis required under § 103 of the patent statute is entirely different than the criteria used to award these prizes.

4. *Assessment of All the Evidence Pertaining to Obviousness.*

In the end, the evidence of secondary considerations of nonobviousness must be weighed with all the other evidence. Otsuka's evidence adds little or no weight to the nonobviousness side of the scales. By contrast, the prior art provides a strong empirical basis for optimizing the prior art carbostyrils to come up with aripiprazole and that weighs heavily on the obviousness side of the scales. When fairly evaluated, the prior art teaches that what you want is a butoxy linker on your carbostyril. That weighs heavily on the side of obviousness. The prior art also teaches that you want chlorine substitution on the phenyl ring of the carbostyril. That, too, weighs heavily on the obviousness side of the scales.

Otsuka fails to refute the desirability of chlorination based on the data available for carbostyril derivatives. Dr. Nichols testified that in 1988 it was generally believed that an electron-withdrawing group was necessary for antipsychotic activity.

> Q. We were talking about chlorination with respect to antipsychotic compounds. Would a person of ordinary skill in the art in October 1988 have believed that chlorine substitution was required for antipsychotic activity?

A. No, not required.

Q. Why not?

A. As of 1988 the general belief was that you required an electron withdrawing group. Chlorine would fall in that group, but there are many others that would also be electron withdrawing.

Q. And can you give any examples of any others.

A. There are compounds with fluorines: trifluoromethyls, sulfonamides, sulfoxides.

(Nichols 1662:7-20.) But Otsuka does not identify the empirical data that would lead to trying fluorines, trifluoromethyls, sulfonamides or sulfoxides on carbostyril derivatives. And certainly it identifies no data that competes with the structure-activity relationship of 2-, 3-, and 4-substituted chlorines provided by the Nakagawa Declaration. (*E.g.*, Press 137:4-14 (explaining that the Nakagawa Declaration data teaches to use chlorines to aripiprazole).)

Then there is the level of ordinary skill in the art, which is one of the required *Graham* findings of fact. There is really no getting around the fact that the level of skill was quite high. Even Otsuka's own chemistry expert Dr. Nichols was surprised at the *Janssen's* case fixing the level of skill at only a master's degree. (Nichols 1528:7-8.); *see Janssen Pharmaceutica N.V. v. Mylan Pharm., Inc.*, 456 F. Supp. 2d 644 (D.N.J. 2006). The evidence overwhelmingly establishes that the PHOSITA has a Ph.D. level of skill both in medicinal chemistry and pharmacology. That high level of skill weighs heavily on the obviousness side of the scales.

Fundamentally, the question in the § 103 obviousness analysis is whether the hypothetical person of ordinary skill had the skill to come up with aripiprazole once given knowledge of the relevant prior art. The evidence shows that aripiprazole was well within the PHOSITA's capabilities no matter which starting point—unsubstituted butoxy, OPC-4392 or dichloro propoxy. The prior art already contained the empirical data necessary to determine the

optimal linker length (butoxy), substitution patterns on the phenyl ring (2,3 position) and linker position on the carbostyril core (7). Indeed, Prof. Castagnoli was right when he testified (Castagnoli 809:8-24) that a research team would have been *negligent* not to have arrived at aripiprazole.

In *KSR*, the Supreme Court explained that "the results of ordinary innovation are not the subject of exclusive rights under the patent laws." 550 U.S. at 427 ("[A]s progress beginning from higher levels of achievement is expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under the patent laws.") The evidence in the prior art pointed the way to aripiprazole. No innovation out of the ordinary was required to follow these sign posts. The asserted claims are, therefore, unpatentable for obviousness under § 103.

The record reveals that what Dr. Oshiro did in "discovering" aripiprazole was at most ordinary innovation. There was no long journey or "aha" moment for Dr. Oshiro to develop aripiprazole. Otsuka's goal was to find a compound that it thought it could get patented. (DTX 268-T at OPC0771184 ("Because a number of similar compounds had already been synthesized, the first hurdle to clear was to find the compounds that could be patented."); Oshiro 1826:20-1827:14).

Otsuka did not "start from scratch." Dr. Oshiro testified that the OPC-4000 series of compounds that included OPC-4139 and OPC-4392 were not new; they had been initially synthesized many years before. (Oshiro 1810:4-1811:2.) Dr. Oshiro did not invent the anti-apomorphine stereotypy test; it was a conventional test as of that time. (Oshiro 1812:1-6.)

Otsuka's story of the invention was made up of steps any person of ordinary skill would have done. Dr. Oshiro took a compound already known to him and made three routine changes:

(1) changing the linker link from a propoxy to a butoxy, (2) substituting chlorine for methyl on the phenyl ring, and (3) using single bonds and double bonds in the carbostyril as alternatives. The only non-routine thing that happened was a labeling mistake which resulted in an incorrect structural assignment. (Oshiro 1828:25-1829:16.) However, even with that setback, it took a mere three months to synthesize aripiprazole. Once Otsuka realized its labeling error and the correct structure, it knew that the substitutions needed were at the 2- and 3-positions (Oshiro 1830:19-1831:1), and aripiprazole was the next compound synthesized. (Oshiro 1833:13-16; Sato Dep. 167:3-13; 167:16 (discussing synthesis of aripiprazole on January 29, 1987).) But for Otsuka's error in labeling, Otsuka would have synthesized aripiprazole immediately. As explained below, the timeline for the development of aripiprazole is short and nothing, if not routine.

The development of aripiprazole began in October 1986 (Oshiro 1827:19-21) when Dr. Oshiro started "[l]ooking to make the best of OPC-4392's characteristic efficacy against the negative symptoms while also having additional efficacy against the positive symptoms." (PTX 33-T at OPC0768530T; Oshiro 1828:17-24.)

During the month of October, as Otsuka explains, Dr. Oshiro told his subordinates to rescreen their existing carbostyril using the stereotypy test—the test that Dr. Roth explained was the same test that had been used to identify every other commercial antischizophrenic drug then known. (Roth 1074:8-1076:7.) Thus, using this known, well-established screening method, Dr. Oshiro's subordinates quickly identified two compounds in addition to OPC-4392 that held promise as useful antischizophrenic agents. (PTX 33-T at OPC0768530-T.) Dr. Oshiro then did some additional investigation regarding structure-activity relationships of these compounds making the very same analysis of the effects of homology (extending the linker length from three

to four carbons), and changing substituents on the phenyl ring. (Oshiro 1765:11-17; 1767:8-12; 1767:19-1768:20; PTX 35-T at 5 (Dec. 1986 Monthly Report) (effect of homology); Oshiro, 1783:6-1786:21; PTX 40-T at 1-2 (Mar. 1987 Monthly Report) (effect of substituent changes).) In fact, Dr. Oshiro's approach in examining the SAR effects of linker length, substituents on the phenyl ring and linker position was routine. He acted just as Defendants' experts said a person of ordinary skill in the art would. For example, the Wise Poster also looked at linker length, substituents on the phenyl ring, and linker position. (DTX 398, Col. 2 (Table 2) (substituents on phenyl ring), Col. 2, (Table 3) (linker position and linker length).) This consideration of the same variable by both Otsuka and the prior art Wise Poster from Parke-Davis is clear and convincing evidence that Otsuka's approach was routine optimization.

Indeed, the prior art was ahead of Dr. Oshiro and already contained SAR information that would have directed a person of ordinary skill in the art to the same place—aripiprazole and similar compounds with methyl, chloro substituents at the 2,3 position on the phenyl ring. The process also would have been sped up had Otsuka labeled its bottles correctly. The work from October to December 1986 was based on the incorrect structure assignment due to the mislabeled bottle. (Oshiro 1829:6-16; 1830:4-6; 1832:2-4.) But for the mislabeled bottle the structure assignment would have been correct, and Dr. Oshiro would have realized that the promising compounds determined from the initial screen were actually 2,3-substituted compounds just like OPC-4392, the 2,3 dichloro propoxy compound of SE '945 and ultimately aripiprazole itself. Otsuka's February 1987 monthly report (PTX 37-T) shows that the labeling mistake was discovered after January 25, 1987. Once the labeling mistake was discovered (PTX 37-T; Sato Dep. 50:13-21), Otsuka synthesized OPC-14597 (aripiprazole) no more than 5 days later on January 29, 1987. (Sato Dep. 167:3-13; 167:16.)

It should be noted that Dr. Oshiro's ultimate conclusions regarding the SAR data that he developed using the stereotypy testing is remarkably consistent with the SAR information already present in the Nakagawa Declaration, Wise Poster and other prior art references concerning the effects of homologation and chlorine substitution on the phenyl ring at the 2 and 3 positions. For example, as Dr. Press and Prof. Castagnoli explained, OPC-4392, the Nakagawa declaration, the Wise Poster and even the Hiyama article concerning OPC-4139 all had the linker attached at the 7 position on the core. (Press 144:21-147:24; 159:8-163:3; Castagnoli 673:5-25; 787:11-13; 792:3-14; 793:19-794:3; 883:15-884:8; 888:11-20; *see* DTX 214; DTX 398; DTX 514.) Therefore, that was an obvious location to attach the linker. Dr. Oshiro, through his testing, similarly determined that the 7 position was best.

With respect to linker length, the Nakagawa Declaration and the Wise Poster both clearly indicated that compounds having butoxy linkers were more potent at blocking the transmission of dopamine in animal studies than were homologous propoxy compounds. Dr. Oshiro similarly concluded that the butoxy was more potent. (Castagnoli 671:18-672:14; 677:4-678:1.)

With respect to substitutions on the phenyl ring, OPC-4392 taught di-substitution at the 2,3 position on the phenyl ring. (Castagnoli 661:7-13; 736:2-6; 753:11-754:6.) The Nakagawa Declaration taught the increase in potency caused by placing chlorines at those positions. The Wise Poster similarly suggested that chlorine at least the 3 position improved potency, and also taught that having a chlorine at that position was more potent than having a methyl at that position. Thus, the motivation was already there to substitute methyls and chlorines at the 2,3 positions. There also was a predicate for dichloro substitution at the 2,3 position with SE '945 specifically exemplifying such a 2,3-dichloro homolog of aripiprazole and the '456 patent teaching an analogous coumarin version of the compound. Both the SE '945 patent application

and '456 patent taught these compounds were expected to exhibit antischizophrenic properties. Additionally, claim 30 of the '416 patent was directed to di-halogenated carbostyril compounds, which would include the 2,3-dichloro compounds. (DTX 6, Col. 72:3-4; Nichols 1716:17-19.)

In sum, the evidence confirms that the last incremental step to aripiprazole from the prior art carbostyrils involved only the "ordinary innovation" that *KSR* says is not patent worthy. 550 U.S. at 427. Accordingly, the asserted claims are invalid for obviousness.

B. THE '416 PATENT DOES NOT "TEACH AWAY" FROM THE UNSUBSTITUTED BUTOXY.

Otsuka's contention that the '416 patent "teaches away" from the unsubstituted butoxy is contrary to the evidence. (*See* OFFCL at 76-83.) Otsuka's argument relies primarily on Dr. Roth's testimony that the '416 patent describes the unsubstituted butoxy as an antihistaminic agent and that a person of ordinary skill would not consider a compound with antihistamininc properties to be a potential antischizophrenic agent. Dr. Roth's testimony on this issue, however, was not credible.

Dr. Roth testified that there is "absolutely no correlation between the ability of a drug to bind to histamine receptors and its antipsychotic activity." (Roth 1387:25-1388:2.) This testimony, however, is inconsistent with Dr. Roth's own "heat map," which establishes that all antischizophrenic agents have antihistaminic activity, indicated by H_1 receptor activity. (PTX 406 at 355; Roth 1224:8-20.) In fact, the heat map shows that aripiprazole has strong H_1 receptor activity.

Dr. Press's testimony on this issue was credible and was consistent with the data in Dr. Roth's heat map. Dr. Press testified that when he was doing antischizophrenic drug research, "antipsychotic agents routinely had some antihistaminic activity." (Press 241:24-242:17.)

Dr. Roth also testified that the halothane anesthesia test described at column 33 of the

'416 patent is not a test for antipsychotic activity. (Roth 1209:22-1210:14.) The testimony of Dr. Oshiro, and an internal Otsuka document, established, however, that Otsuka itself used the halothane anesthesia test as a screening test for antischizophrenic activity. (Oshiro 1846:21-1848:6; DTX 208, 208-T.)

Dr. Press testified credibly that a medicinal chemist would understand based on the specification of the '416 patent that the patent is directed to carbostyril derivatives that can be used as antischizophrenic agents. (Press 120:15-121:5; 123:25-124:5.) In particular, the '416 patent describes a number of tests that those working in the field would recognize as animal tests for schizophrenia, including the apomorphine vomiting inhibitory action test, the spontaneous movement controlling action test, hyper-motion controlling action of rats, antimethamphetamine action, and methamphetamine group toxicities. (Press 121:6-122:22; DTX 6, Col. 3:3-17.) As Dr. Press testified, "[t]hose are all tests that have been used in laboratories looking for antischizophrenic agents." (Press 122:21-22.) Dr. Press's group actually used several of the tests while he was engaged in antischizophrenic drug research at Lederle. (Press 122:23-123:3.)

Otsuka's argument that there is no evidence that the compounds of the '416 patent were actually tested in the tests listed in the patent amounts to an argument that Otsuka's representations in the specification of the '416 patent were false. (*See* OFFCL at 80.) As Dr. Press testified when asked about the antischizophrenic tests listed in the '416 patent, "as one of skill reading this, one assumes that in a patent application the inventors are telling the U.S. Patent Office what they've done and how these compounds would be useful." (Press 227:10-13.) Dr. Press went on to testify that, in his understanding, Otsuka "would not be being honest with the patent office if they listed tests that they had not used." (Press 226:20-23.)

C. THE NAKAGAWA DECLARATION WOULD LEAD THE PERSON OF ORDINARY SKILL TO START WITH THE UNSUBSTITUTED BUTOXY.

Otsuka's attempts to have the Court view the teachings of the '416 patent in isolation is inconsistent with 35 U.S.C. § 103, which requires that the prior art be "viewed as a whole." In this case, the prior art Nakagawa Declaration would teach the person of ordinary skill that the unsubstituted butoxy has antischizophrenic activity. Indeed, of all the compounds disclosed in the '416 patent, the unsubstituted butoxy was among the handful chosen by Otsuka to test in the mouse jumping test.

Otsuka attempts to convince the Court that the mouse jumping test would not have been viewed as a test for antipsychotic activity, but all the evidence is to the contrary. (*See* Defendants' Post-Trial Proposed Findings of Fact and Conclusions of Law ("DFFCL") at Section III(E)(1)(a).) Tellingly, Otsuka's expert Dr. Nichols clearly admitted under questioning from the Court that Otsuka used the mouse jumping test in the Nakagawa Declaration "as a predictor of potential antipsychotic activity." (Nichols 1642:5-9.)

Otsuka's principal argument is that the person of ordinary skill in the art looking at the Nakagawa Declaration would have chosen compound 44 as a lead compound over the unsubstituted butoxy. (*See* OFFCL at 87-90.) Defendants' experts acknowledged that compound 44 was the most potent, but explained why the person of ordinary skill would not have pursued it in the first instance. First, as Dr. Press testified, compound 44 is a 5-isomer compound (linker attached to the 5 position of the carbostyril ring) whereas the unsubstituted butoxy is a 7-isomer compound (linker attached to the 7 position of the carbostyril ring). (Press 160:22-164:22.) The compounds that Otsuka had reported in the literature, OPC-4392 and OPC-4139, were 7-isomer compounds. (Press 144:21-146:17.) Dr. Press explained that medicinal chemists would not try to change the substitution on the core because that would be a

significant change to the prior art carbostyril compounds that had previously been described in the literature and tested in humans. (Press 160:22-164:22 at 162:16-163:13.) Dr. Press demonstrated with a three-dimensional model that if you change the point of attachment of the linker (from 7 to 5), you change the relationship of the nitrogens of the piperazine to the nitrogen of the carbostyril. (Press 163:17-164:10.) None of Otsuka's experts rebutted this testimony.

Dr. Castagnoli testified that compound 44 has an ethoxy group at the 2 position and that there was very strong evidence in the prior art that introducing an ethoxy group would lead to potent alpha-1 blocking activity, which is an indication of the side effect of orthostatic hypotension. (Castagnoli 787:14-25.) As Dr. Roth testified, orthostatic hypotension is a serious side effect of antipsychotic drugs. (Roth 1049:6-9; 1090:8-23.) Dr. Castagnoli explained that, based on the data in the prior art '932 patent, the person of ordinary skill would conclude that "the ethoxy group should not be incorporated into any compound in this series that is intended for human use." (Castagnoli 789:7-790:17.)

Dr. Castagnoli's testimony is confirmed by the real world evidence of which compounds Otsuka decided to pursue. Otsuka's data on the 2-ethoxy compounds confirmed that they perform very poorly in the anti-epinephrine test, meaning an increased liability for orthostatic hypotension. (Oshiro 1817:22-1818:7.) Otsuka chose not to develop the 2-ethoxy compound, even though it had good results in the anti-apomorphine stereotypy test for antipsychotic activity. (Oshiro 1821:3-7.)

Moreover, the disclosure of alternatives in the prior art does not amount to "teaching away," as Otsuka suggests. A finding that the prior art "teaches away" requires a showing that the prior art teaches that the selected compound is unlikely to produce the objective of the claimed invention. *See In re Dunn*, 349 F.2d 433, 438 (C.C.P.A. 1965); *Syntex (U.S.A.) LLC v.*

Apotex, Inc., 407 F.3d 1371, 1380 (Fed. Cir. 2005); *In re Peterson*, 315 F.3d 1325, 1332 (Fed. Cir. 2003); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 425-26 (2007) (teaching away not found where there was no indication that the prior art was "somehow so flawed that there was no reason" to modify it). Here, the mere fact that compound 44 might also be a potentially interesting compound based on the Nakagawa Declaration data does not amount to a "teaching away" from the unsubstituted butoxy.

Not only has Otsuka failed to show any teaching away from the unsubstituted butoxy, Otsuka's argument that aripiprazole exhibited unexpectedly superior potency in the stereotypy test over the unsubstituted butoxy is unavailing. (*See* OFFCL at 132.) Otsuka contends that because in one stereotypy test the unsubstituted butoxy had an ED_{50} value of >28, indicating that the compound had no potency at the single dose of 28 µmol/kg tested, that aripiprazole necessarily is unexpectedly superior. (PTX 564 at 661.) First, the Nakagawa Declaration taught that adding chlorines to the unsubstituted butoxy would have increased its antipsychotic potency. (*See* Section I(B)(2).) Therefore, one of skill in the art would have *expected* aripiprazole, which has two chlorines, to have greater potency than the unsubstituted butoxy, which has no chlorines. Second, Otsuka has presented no evidence that the unsubstituted butoxy would not have potency in the stereotypy test at a higher dosage. Clozapine, which Dr. Roth testified is the "gold standard" and the "best" antipsychotic, for example, is generally considered inactive in the stereotypy test, but Otsuka was able to calculate an ED_{50} value for clozapine at a very high dose of 34.5 mg/kg, which is higher than 28 µmol/kg. (Roth 1343:1-19; 1339:12-1340:2; DTX 1556 at 2 (indicating that clozapine has a molecular weight of 326.83).) Third, even though the FDA-approved package insert for clozapine indicates that clozapine has no potency in the stereotypy test, Otsuka has not claimed that aripiprazole has unexpectedly superior potency over clozapine.

In fact, Dr. Roth considers clozapine to be a better antipsychotic than the atypical antipsychotics, including aripiprazole. (Roth 1334:23-1335:7.) For these same reasons, Otsuka has not demonstrated that aripiprazole exhibited unexpectedly superior potency in the stereotypy test over OPC-4392. (*See* OFFCL at 132-33.)

D. THE WISE POSTER IS ADMISSIBLE.

Otsuka again challenges the status of the Wise Poster (DTX 398) as a prior art printed publication under 35 U.S.C. § 102(b), claiming that there is insufficient corroboration. Previously, Otsuka had raised an evidentiary objection to the Wise Poster's authenticity. Dr. Wise's deposition testimony[4] more than adequately authenticates the document. Dr. Wise provided all the testimony necessary to authenticate the Wise Poster. Dr. Wise testified about the creation of Exhibit 1 at his deposition. (Wise Dep. 45:5-12; 46:6-47:13.) He testified about his retention of a copy of the handout distributed at the 1987 meeting. (Wise Dep. 48:13-15; 49:5; 49:7-19; 50:9-51:10.) This testimony was gone over again, in more detail in Defendants' taking of Dr. Wise's testimony after Otsuka had finished its initial questioning. It reiterated that the copy of the Wise Poster at the deposition was presented in New Orleans (Wise Dep. 65:14-17; 66:5-6), that it was kept in Dr. Wise's personal files (Wise Dep. 66:7-11), and that a copy of the Wise Poster was given to Defendants during Dr. Wise's work as a consultant for them (Wise Dep. 66:19-67:15; 68:9).

Otsuka has now cited to *TypeRight Keyboard Corp. v. Microsoft Corp.*, 374 F.3d 1151

[4] Contrary to Otsuka's assertions, Otsuka was not obstructed in its questions of Dr. Wise. Otsuka was to take the deposition of Dr. Wise for the limited purpose of authenticating the Wise Poster. (Eighth Pretrial Scheduling Order, D.I. 300 ("Dr. Wise's testimony shall be confined to foundational testimony concerning the authenticity and alleged prior art status of the Wise Poster.").) Otsuka questioned Dr. Wise on whether the poster they had was the one he presented at the meeting and was told that it was. (Wise Dep. 40:4-14.) It was an answer they got more than once. (Wise Dep. 44:2-6.) The fact Otsuka questioned Dr. Wise beyond the limited scope of the deposition and was met with proper objections by Defendants' counsel does not amount to obstruction.

(Fed. Cir. 2004), in an effort to show that corroboration is sometimes required for a printed publication. In *TypeRight* the document in question required corroboration because it was undated. Here, the Wise Poster is dated and shows on its face that it was presented during the Society for Neuroscience conference in 1987. (DTX 398.) Therefore, as explained in Defendants' opening submission, no corroboration was required.

In *TypeRight* the Court of Appeals reversed a finding of summary judgment because genuine issues of fact remained over the credibility of witnesses who testified that the document had been publicly distributed as of a particular date. *TypeRight*, 374 F.3d at 1158. The witnesses were not the authors and had only vague and equivocal recollections about the document and its distribution. *Id.* at 1158. Further, the date that the witnesses ascribed to the document was inconsistent with date of the file from whence the document was produced and also conflicted with the dates of the authors' patenting activities.

There are no similar credibility problems here following full trial on the merits, even if corroboration were required. Otsuka deposed Dr. Wise, the lead author of the Wise Poster, and he testified credibly and in great detail at his deposition regarding the display of the Wise Poster at the 1987 Society for Neuroscience conference in Louisiana. Dr. Wise's testimony, which has been designated and is part of the record in this trial, is consistent with the document itself and also with Otsuka's own internal Haruki Memo and with other circumstantial evidence, which confirms that the Wise Poster was part of the 1987 Society for Neuroscience conference. In short, as stated in Defendants' Proposed Findings of Fact and Conclusions of Law, there is no need for corroboration under these circumstances; however, even if there were, in this case there is sufficient corroboration that the Wise Poster is indeed 35 U.S.C. § 102(b) prior art.

1. *If Corroboration Were Required, Dr. Wise's Testimony About the Wise Poster Is Corroborated Under a Rule of Reason Analysis.*

a. The Rule of Reason Analyzes All Available Evidence to Prevent Fraud from Oral Testimony.

To the extent corroboration is required for the Wise Poster, it is present here. Corroboration is evaluated under a rule of reason analysis. *Kridl v. McCormick*, 105 F.3d 1446, 1449 (Fed. Cir. 1997); *Price v. Symsek*, 988 F.2d 1187, 1195 (Fed. Cir. 1993). The rule of reason has been developed over the years to ease the requirement of corroboration. *Coleman v. Dines*, 754 F.2d 353, 360 (Fed. Cir. 1985). The corroboration requirement exists to prevent fraud. *Kridl*, 105 F.3d at 1450 (citing *Berry v. Webb*, 412 F.2d 261, 266 (C.C.P.A. 1969)). The credibility of testimony is determined based on an evaluation of "*all* pertinent evidence." *Price*, 988 F.2d at 1195 (emphasis in original); *Kridl*, 105 F.3d at 1450; *Berry*, 412 F.2d at 266-67. The absence of contradiction and internal conflict strengthens the ability of testimony to meet the rule of reason. *Kridl*, 105 F.3d at 1450.

b. The Surrounding Facts Provide Objective Evidence That the Wise Poster Was Presented at the 1987 Conference of the Society for Neuroscience.

Dr. Wise in his designated deposition testimony provides undisputed testimony regarding the presentation of the Wise Poster. In addition to his testimony, there are several exhibits that tie Dr. Wise to the introduction of PD 116,795 to the scientific community in 1987 through the Wise Poster.

The '456 patent (DTX 629) lists Dr. Wise as an inventor. Example 1 of the '456 patent discloses the name and structure of PD 116,795 which is the same compound highlighted on the Wise Poster. (DTX 629, Col. 10:45-46.) Additionally, the '456 patent corroborates other compounds disclosed in the Wise Poster that formed the basis for Profs. Marshall's and Castagnoli's testimony. The '456 patent had the compounds from Table 2 of the structure-

activity relationship portion of the Wise Poster: (1) 4-Cl is at Col. 11:44-45; (2) 4-CH_3 is at 11:40-41; (3) 3-Cl is at 11:42-43; (4) 3-CH_3 is at 11:38-39; (5) 2-OCH_3 is at 12:21-22; (6) 2-CH_3 is at 11:30-31. Also, the unsubstituted butoxy compound of Table 3 can be found in the '456 patent. (DTX 629, Col. 11:32-33.)

As discussed at length in Defendants' Proposed Findings of Fact and Conclusions of Law, Otsuka's own September 1988 Haruki Memo agrees that PD 116,795 was reported at the 1987 conference in Louisiana. (DTX 274-T at OPC0730595 ("we have not obtained any detailed reports since it was reported at the Society for Neuroscience (Louisiana, US) last year").) Otsuka does not dispute that the Parke-Davis compound PD 116,795 was announced as a dopamine agonist at the Society for Neuroscience conference in Louisiana in 1987. In fact, Otsuka does not really dispute that the Wise Poster was a source of the information included in the Haruki Memo. Otsuka instead argues, without offering any other potential sources for the information, that the Wise Poster may not "have been the only source of information included in the Haruki Memo." (OFFCL at 191.)

There are too many similarities between the information disclosed in the Wise Poster and the information in the Haruki Memo to dismiss the Wise Poster as the source of the information. A summary of information about PD 116,795 attached to the Haruki Memo confirms the close alignment of what was known and recorded by Otsuka prior to the critical date and what Wise said he disclosed.

1. Both the Wise Poster and the Haruki Memo refer to PD 116,795 identically.

2. The name given at the beginning of the abstract of the Wise Poster and the name given at the beginning of the Otsuka summary in the Haruki Memo are identical, both using the benzopyranone option for naming the compound, and not the coumarin name.

3. Both the Wise Poster and the Haruki Memo agree that the work comes from

> Parke-Davis research.
>
> 4. Both the Wise Poster and the Haruki Memo agree that PD 116,795 is a dopamine autoreceptor agonist.
>
> 5. Both the Wise Poster and the Haruki Memo agree that PD 116,795 inhibits spontaneous locomotor activity in rats and mice, and in fact both use the exact same numbers and routes of administration: 2.59 mg/kg i.p. for mice and 2.1 mg/kg after oral administration (oral and p.o. are the same: Marshall 371:21-372:12; Beninger 927:10-928:13).
>
> 6. The Otsuka summary of PD 116,795 in the Haruki Memo also agrees with the Wise Poster regarding the abstract citation in the upper left corner of the Wise Poster. It agrees on (1) the abstract number: 128.9; (2) the publication name for the abstract: the Wise Poster has "Soc. Neurosciences Abst." and the Haruki memo has "SOC NEUROSCI ABST"; (3) the volume of the publication, which the Wise Poster has as "13" and the Haruki Memo has "13(1)"; (4) and the year 1987. (DTX 274-T at OPC0730596.) It also confirms the connection between the '456 patent and PD 116,795 (and thus the Wise Poster) by having "US 4701456" written on the page. (*Id.*)

The fact that the Wise Poster contains the same data as the summary of PD 116,795 in the Haruki Memo (the 2.59 and 2.1 numbers) directly contradicts Otsuka's argument that the existing corroboration does not include data from the Wise Poster that is relied upon by Defendants in making their arguments. The value of 2.59 in the abstract of the Wise Poster is rounded off to one decimal place as the number "2.6" in the first line of the third column of the table "2. Incorporation of Substituents on the Phenyl Ring Results in Loss of DA Agonist Activity." This data is central to the butoxy-is-superior-to-propoxy argument and is relied upon by both Profs. Marshall and Castagnoli in their testimony about the Wise Poster. (Marshall 364:10; Castagnoli 676:23-25.)

c. The Facts Before the Court Are Distinguishable from *TypeRight*.

The facts of the present case are readily distinguishable from *TypeRight*, and clearly and convincingly establish that the Wise Poster was presented and distributed at the November 1987 Society for Neuroscience conference. In *TypeRight*, which the Federal Circuit described as a

"close case," the questions regarding the credibility of the testimony supporting the document in question stemmed from many factors that are not present here. *Id.* at 1157.

First, the document in question in *TypeRight* was undated and the party propounding the document failed to check with the originator of the document to attempt to definitively date the document. *TypeRight*, 374 F.3d at 1158. Here, the Wise Poster bears a 1987 date and the author, Dr. Wise, confirmed the accuracy of that date.

Second, the testimony concerning the document in *TypeRight* was tentative and contained inconsistencies. *TypeRight*, 374 F.3d at 1158 ("the testimony itself was somewhat tentative. Dr. Hirsh testified only that he remembered seeing photographs 'similar' to [the document] being distributed at a 1986 trade show."). For example, there was a discrepancy between the 1986 date asserted by a witness and the 1990 date of the file that the witness had kept the document in that raised questions about the accuracy of the testimony. *Id.* at 1158. The discrepancy had no explanation. *Id*. Further, if the ascribed date of the document were correct, it would potentially invalidate two of the author's own patents, which were only applied for after the alleged public disclosure. *Id.* All of these raised questions about the accuracy of the witnesses' memory.

Here, although the document was from 1987, the testimony was detailed and unequivocal. Dr. Wise testified that DTX 398 was one of the very handout-sized copies (not the large poster) that were handed out at the conference.

> Q. Can you describe in general what your poster looked like?
>
> A. Yes. I know exactly what it looked like. It looks exactly like the hand-outs that you all have today. That is a duplicate of it.
>
> It was made by a photographic process. So the poster and the hand-outs were the same, they were identical.
>
> This was made by a mechanical means in the 1980s in which it was all mounted on a white board and it was photographed. And then the photograph was

> developed into a very large one used as a poster and also a small one which was used for hand-outs.
>
> So what you see on the small one was exactly what was up on the board.

(Wise Dep. 22:18-23:11.)

Dr. Wise also testified that he kept the document in a binder in chronological order along with other documents of the same type. (*Id*. at 49:7-19.) He gave reasons for why he kept close track of his record of scientific publication—the "publish or perish" mentality of scientists. (*Id*. at 50:9-51:10.) The many CVs in this case (DTX 1428; DTX 1431; DTX 1441; PTX 108; PTX 400; PTX 556) indicate to the Court that such recordkeeping is routine for people in the art. Beyond his recordkeeping, Wise remembered details of the 1987 meeting. For example, he specifically remembered that it was his first time in visiting New Orleans. (Wise Dep. 12:16-13:4.) Furthermore, the timing of the Wise Poster is consistent with Parke-Davis's patenting activities. The '456 patent was applied for in 1985 (DTX 629 at cover), and PD 116,795 was introduced to the scientific community at the 1987 Society for Neuroscience conference.

In *TypeRight*, issues were raised concerning the potential bias of the testifying witnesses who had been compensated for their time. *TypeRight*, 374 F.3d at 1158. However, here, in addition to Dr. Wise's unrefuted testimony, the Wise Poster also is corroborated by Otsuka's own internal documentation in the form of the Haruki Memo, DTX 274-T. The Haruki Memo confirms details about the Wise Poster, and states that PD 116,795, one of the compounds discussed in the Wise Poster, was "reported" at the 1987 conference. On the second page of the prior art Haruki Memo, it identifies Dr. Wise as the author of the pharmacological data they recorded. (DTX 274-T at OPC0730596 ("PHARMACOLOGY: WISE, J.D. ET AL.").) Otsuka has offered no evidence making the Wise Poster inconsistent with what is known about the reporting of PD 116,795 at the conference.

The evidence that Otsuka points to in an effort to cast doubt on Dr. Wise's credibility is weak. For example, Otsuka asserts that Dr. Wise could not recall the names of people who might have visited his booth during the 3 ½ hours the Wise Poster was on display at a conference attended by more than eleven thousand people. This is hardly surprising and does nothing to discredit his undisputed testimony that he did in fact display the Wise Poster and distribute miniature duplicates as handouts. Otsuka also raises the issue of an e-mail sent by Dr. Wise to Defendants' counsel stating he was not certain that the Wise Poster was presented. (OFFCL at 193.) Otsuka fails to mention that when Dr. Wise was questioned about why he was more certain in his deposition testimony than he was in the e-mail, he explained that he was being cautious about what he said until he had reviewed his records. (Wise Dep. 54:21-56:3 ("Before I unequivocally stated this I had to look to make sure that it was correct. I was being careful" and "Well, I was not a hundred percent sure before I actually looked. I assumed it, but I was being careful.").) Dr. Wise reviewed his records and was able to determine that the Wise Poster was presented in November 1987 and the e-mail does not undermine the credibility of Dr. Wise's testimony.

2. *Dr. Wise's Deposition Testimony Is Admissible and Not Hearsay.*

Otsuka cites no authority for its objection to Dr. Wise's deposition as being inadmissible hearsay. Federal Rule of Civil Procedure 32 overcomes the hearsay objection.

Defendants satisfy Rule 32's requirements, and thereby obtain a complete defense to Otsuka's objection. *United States v. Vespe*, 868 F.2d 1328, 1339 (3d Cir. 1989). Defendants satisfy each of Rule 32's requirements. Otsuka had two attorneys at the deposition satisfying the representation requirements of Rule 32(a)(1)(A). Dr. Wise gave his address as being in Ann Arbor, Michigan. (Wise Dep. 8:10-11.) The Court can take judicial notice that Michigan is separated from New Jersey by Pennsylvania and Ohio, and is indeed more than 100 miles from

Trenton, New Jersey. Accordingly, Rule 32(a)(1)(C) is satisfied by Rule 32(a)(4)(B). Further, while Otsuka has observed that Defendants did not bring Dr. Wise to trial, they have provided no evidence that Defendants procured Dr. Wise's absence as required by the last clause of Rule 32(a)(4)(B). Procuring absence and doing nothing to facilitate presence are quite different things. *Carey v. Bahama Cruise Lines*, 864 F.2d 201, 204 (1st Cir. 1988) (quoting *Houser v. Snap-on Tools Corp.*, 202 F. Supp. 181, 189 (D. Md. 1962)). Furthermore, Otsuka did not complain to the Court about needing Dr. Wise's testimony.

Otsuka's reliance on *Derewecki v. Pennsylvania Railroad Co.*, 353 F.2d 436 (3d Cir. 1965) and *United States v. Alvarez*, 2010 U.S. Dist. LEXIS 2456 (D.N.J. Jan. 13, 2010) is unavailing. (*See* OFFCL at 188.) As the Third Circuit noted in footnote 7 of *Derewecki*, Rule 26(d)(3), the predecessor rule to Rule 32(a)(4)(B),[5] permitted the proponent of the deposition testimony to offer the testimony into evidence if the deponent lived more than 100 miles away, just as in this case. *Derewecki*, 353 F.2d at 441 n.7 ("Rule 26(d)(3) also provides for free use when: []2, that the witness is at a greater distance than 100 miles from the place of trial or hearing, or is out of the United States"). *Alvarez* was about whether it was an "exceptional circumstance when the interests of justice require[d] . . . [the] court to authorize a deposition in a criminal case." *Alvarez*, 2010 U.S. Dist. LEXIS 2456, at *10. That is not the issue in these proceedings.

3. *Otsuka's Reliance on Other Authority Is Misplaced.*

Otsuka invokes other authorities involving facts different from the case at bar. Otsuka relies upon *Lister*, but the section it cites is about databases being updated, not about the presentation and distribution of materials at a scientific meeting. *In re Lister*, 583 F.3d 1307,

[5] *See* Fed. R. Civ. P. 32 advisory committee's note (1970 Amendment: "As part of the rearrangement of the discovery rules, existing subdivisions (d), (e) an (f) of Rule 26 are transferred to Rule 32 as new subdivisions (a), (b), and (c).").

1316-17 (Fed. Cir. 2009) ("In contrast, in this case the government has not identified any evidence of the general practice of the Copyright Office, Westlaw, or Dialog with regard to database updates."). Otsuka also advances *In re Omeprazole Patent Litigation*, 536 F.3d 1361, 1381 (Fed. Cir. 2008), but in *Omeprazole* the sponsoring witness for the brochure could not testify about the distribution of the brochure. *Id*. ("The employee could not, however, provide information about the circulation and availability of the brochures in the 1960s or 1970s, the period during which the brochures were produced."). Dr. Wise testified about those factors here. *Norian Corp. v. Stryker Corp.*, 363 F.3d 1321, 1330 (Fed. Cir. 2004), also does little to assist Otsuka's argument. In *Norian*, the document was not distributed at a conference, but only available if requested, and there was no evidence that the document was ever requested. *Id*. ("Norian argued that the Abstract did not meet the criteria of § 102(b) because it was available only upon individual request to the authors, and that such request and dissemination had not been shown."). By contrast, the evidence here is that the Wise Poster was at the 1987 scientific conference, not that it was kept back at Parke-Davis, and that numerous copies were handed out. Defendants' case has none of the deficiencies that resulted in those other courts finding a lack of corroboration.

E. DEFENDANTS' EXPERTS WERE WELL QUALIFIED.

Otsuka again seeks to criticize Defendants' experts' qualifications, particularly because they were not medical doctors. This issue was extensively briefed and dealt with in pretrial motion in limine filings, (D.I. 319; D.I. 326) which will not be rehashed here. Nevertheless, this argument is particularly ironic post trial given that Otsuka relied extensively on the testimony of an *economics* expert, Dr. Jarosz, to try to support its secondary considerations arguments concerning the allegedly unique side effect profile of aripiprazole as compared to other antipsychotic drugs on the market. (*E.g.*, Jarosz 2048:9-22.) Suffice it to say that both sides

agree that a person of ordinary skill in the art here is a scientist—with knowledge of medicinal chemistry and pharmacology, not a medical doctor. What matters is how the scientist would interpret and understand the clinical data, not a medical doctor. Defendants' experts have fairly interpreted the test data in rendering their opinions.

F. OPC-4392 WAS A RESEARCH SUCCESS THAT LAID THE GROUNDWORK FOR ARIPIPRAZOLE.

Dr. Oshiro gave a presentation in 2006 in which he stated that OPC-4392 "is the origin of the development of aripiprazole." (DTX 268-T at OPC0771177; Oshiro 1797:14-18.)[6]

Repeatedly in its arguments, Otsuka says to ignore what the documents conclude about OPC-4392 and its properties and instead rely on Dr. Roth's interpretation. As pointed out during his cross-examination, Dr. Roth has been a paid consultant of both Otsuka and its marketing partner with respect to aripiprazole, Bristol-Myers Squibb. (Roth 1293:5-21.) Dr. Roth also admitted that Otsuka had entered into an agreement involving more than $100 million in funding to support Galenea Pharmaceuticals, with which Dr. Roth has a royalty sharing agreement. (Roth 1293:22-1294:15; 1295:4-16.) In spite of his involvement with Otsuka and aripiprazole, and his years as a practicing physician, Dr. Roth has not prescribed aripiprazole. (Roth 1295:22-24.) Thus, while Dr. Roth calls some of the data concerning OPC-4392 a "red flag," the authors of articles that Otsuka cites—which were authored by Otsuka scientists and doctors such as Dr. Murasaki who were working with Otsuka—concluded that OPC-4392 was both safe and promising as an antischizophrenic drug. For example, with respect to PTX 545, the results of the Phase I study of OPC-4392 that Dr. Roth termed a "red flag," the authors concluded:

> Judging from the results of the present study, OPC-4392 was ascertained to be safe and have conspicuous characteristics, which had quite a different effect upon the serum prolactin level from that of conventional antipsychotic drugs.

[6] There was some discussion of the proper translation for the Japanese word "moto." Dr. Oshiro testified that it could be translated as "cause" rather than "origin." (Oshiro 1800:3-12.)

> Therefore, OPC-4392 is expected to have some advantageous effects different from those of conventional antipsychotic drugs.

(PTX 545 at 802; Roth 1405:9-1406:23.)

Dr. Roth's testimony concerning OPC-4392 was inconsistent with the real world evidence as to how researchers in the field viewed OPC-4392. As Dr. Oshiro testified, Otsuka developed OPC-4392 as a treatment for schizophrenia. (Oshiro 1801:13-16; PTX 34-T at OPC0768534.) Dr. Oshiro reported in an internal Otsuka document that the Phase II trials showed that OPC-4392 was "effective on the negative symptoms but weak on positive symptoms." (Oshiro 1802:11-19; PTX 34-T at OPC0768534.) Dr. Oshiro testified that the results of the Phase II trials showed that OPC-4392 did not cause EPS side effects and did not increase prolactin levels. (Oshiro 1803:7-20.) In fact, Dr. Oshiro's goal was to develop a compound that was as effective as OPC-4392 on negative symptoms but more effective on positive symptoms. (Oshiro 1807:21-1808:4.)

Contrary to Dr. Roth's testimony, OPC-4392 had some D_2 antagonist activity. (PTX 35-T at OPC0768541; Oshiro 1812:25-1813:2.)

As of February 1988, OPC-4392 was still in Phase III clinical trials and Otsuka intended to apply for its approval as an antischizophrenic drug. (DTX 322-T at 1; Oshiro 1805:5-14.)

Although Dr. Roth repeatedly termed OPC-4392 an abject "failure," it went on from Phase I trials to Phase II trials and was still promising enough after Phase II trials to make it to Phase III clinical trials. (Roth 1411:19-23; 1412:15-1414:6; DTX 362-T; DTX 388-T at 1517.) Dr. Roth also strained to find the negative in DTX 394, the Gerbaldo article, which reported that OPC-4392 treated hallucinations, a positive symptom of schizophrenia, in 4 out of 4 patients. (DTX 394 at OPC0757398; Roth 1418:5-1419:9.) To be sure, OPC-4392 was not perfect. That provided motivation to persons of ordinary skill in the art to improve upon its properties—to take

OPC-4392's good profile regarding its treatment of negative symptoms of schizophrenia, its lack of toxicity and good side-effect profile (no EPS, no hyperprolactinemia, no orthostatic hypotension, no tardive dyskinesia), and to improve upon its ability to treat positive symptoms by increasing its potency. (Castagnoli 644:7-23; 658:14-659:3; 754:14-755:3; 803:11-804:3.) As the Federal Circuit in *Medichem S.A. v. Rolabo, S.L.*, aptly explained:

> As we have explained above, the fact that some teachings in the prior art conflict with others does not render the findings of the district court clearly erroneous per se. Rather, **the prior art must be considered as a whole for what it teaches**. We understand the prior art, viewed as a whole, to **teach that the addition of a tertiary amine sometimes works to improve the yield** of McMurry reactions, especially when a tertiary amine is used in relatively low concentrations. In light of this, we cannot say that the district court clearly erred in finding that the prior art would have provided the skilled artisan with a motivation to combine references so as to use pyridine in the McMurry reaction.

437 F.3d 1157, 1166-67 (Fed. Cir. 2006) (emphasis added).

Otsuka devotes space in its submission touting the mixed dopamine agonist/antagonist properties of aripiprazole. (*See* OFFCL at 50.) But that characteristic does not distinguish aripiprazole from the prior art—particularly OPC-4392, which also was known at the time and thereafter to be a presynaptic dopamine D_2 receptor agonist and a postsynaptic dopamine D_2 antagonist. (Roth 1401:23-1404:23; 1420:13-1421:21; DTX 104 at OPC0791807-08; *see also* DTX 396 at 180 ("The broadly comparable neuroendocrine profiles of SDZ HDC-912 and OPC-4392 suggest a DA partial agonist action of these two compounds. Contrary to classical neuroleptics, SDZ HDC-912 and OPC-4392 decrease PRL basal level, which is in favor of a DA agonist action. However, like classical neuroleptics, they block PRL response to Apo, which is consistent with a DA antagonist effect. This new category of atypical antipsychotic drug could represent a promising alternative in the treatment of schizophrenic syndromes.").)

G. IF THE COURT WERE TO ACCEPT OTSUKA'S POSITION THAT OPC-4392 WAS SUCH A FAILURE THAT NO ONE WOULD THINK CARBOSTYRILS COULD BE USED TO TREAT SCHIZOPHRENIA, THEN THE ASSERTED CLAIMS WOULD BE INVALID UNDER §§ 101 AND 112.

Otsuka's position is that OPC-4392 was such a failure that it poisoned the well for thinking that any carbostyril could be used to treat schizophrenia. For example, Otsuka says (OFFCL at 73) that there was "no scientific basis for a person of ordinary skill in the art in October 1988 to conclude that OPC-4392 *or any other carbostyril derivative* would be a therapeutically effective antipsychotic drug. [Roth 1205]" (emphasis added) (citation to Dr. Roth by Otsuka). Here is the cited portion of Dr. Roth's testimony:

> Q. Based on the information you have reviewed, Dr. Roth, was there any scientific basis for a person of ordinary skill in the art in October 1988 to conclude that any other carbostyril derivative would be a therapeutically effective antipsychotic drug?
> A. No.

(Roth 1205:17-22) If the Court were to find that Otsuka is correct on this point, then the legal consequence would be that the asserted claims are invalid for failure to meet the utility requirement of 35 U.S.C. § 101 and/or the enablement requirement of § 112. *In re Ziegler*, 992 F.2d 1197, 1200 (Fed. Cir. 1993) ("The how to use prong of section 112 incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention."). There would be invalidity under §§ 101/112 because there is nothing in the '528 patent that would have changed the mind of a skilled person who (if one accepts Otsuka's view) was already of the belief that carbostyrils were not suitable for treating schizophrenia.

The fact that the FDA has approved aripiprazole for the treatment of schizophrenia does not settle the §§ 101/112 issue. The question is not whether aripiprazole in fact is useful to treat schizophrenia; rather, the question is whether the *content of the patent's written description* was

sufficient to establish in the mind of a person of ordinary skill that the claimed invention had that utility. *Janssen Pharmaceutica N.V. v. Teva Pharm. USA, Inc.*, 583 F.3d 1317 (Fed. Cir. 2009) (holding patent on a drug approved by the FDA for the treatment of Alzheimer's disease invalid because patent application disclosed insufficient to establish usefulness for that purpose); *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 676 F. Supp. 2d 352, 371 n.14 (D.N.J. Dec. 31, 2009) ("The *utility in-fact* of the claimed method *is not disputed*. *The utility requirement* for patentability, *however, requires that utility properly be disclosed in the patent*. Regardless of whether doctors at MGH and experts at the FDA recognized the invention's utility, without providing the PTO with evidence of such recognition, Plaintiff cannot show that the patent credibly discloses utility.") (emphasis added) (summary judgment denied), *reconsideration denied*, No. 07-cv-3770 (DMC), 2010 WL 715411 (D.N.J. Feb. 23, 2010), *final judgment*, 2010 WL 3210516, at *35 (D.N.J. Aug. 12, 2010), ("Although this Court recognized the utility in fact of the invention, the Court determined that these results (or the initiation of the trials) could not serve to demonstrate utility because the materials were not disclosed to the patent office.") (holding patent invalid under §§ 101/112).

The '528 patent has *no human data*. (Nichols 1726:20-22.) It only has animal testing data from two tests, only one of which (the anti-apomorphine stereotypy test) even arguably correlates to antischizophrenic potency. (Nichols 1726:23-1728:9.) That test was known to sometimes yield false positives. (Marshall 2188:22-2189:3.) In any event, it is undisputed that human testing trumps animal testing because only humans have schizophrenia. Here is what Otsuka says about that:

> The rodent studies, however, would have been essentially irrelevant in October 1988 because by then the unsuccessful clinical results *in humans* had already been published for OPC-4392. [PTX 545; DTX 990] A person of ordinary skill in the art in October 1988 would have been more interested in clinical studies of OPC-

> 4392 in humans rather than preclinical studies in rodents. [Roth 1187] Defendants themselves acknowledge that "human trials trump animal studies." [Def. FOFCOL, page 113]

(OFFCL at 73 (italics and citations by Otsuka).)

Otsuka's arguments, if accepted, would invalidate the asserted claims because, per Otsuka, in 1988 the alleged "failure" of OPC-4392 in clinical trials would have led those skilled in the art to believe that all carbostyrils would not work as antischizophrenic agents and that success in mere animal testing would be trumped by the alleged "failures" in human testing testing. Invalidity would be readily apparent with respect to Claims 17 and 23 because they specifically recite treatment of schizophrenia.

Claim 12 is for the compound aripiprazole, without the recitation of any particular utility. The only utility actually mentioned in the '528 patent is the treatment of schizophrenia. If that is the utility alleged to support Claim 12, then invalidity follows for the reasons mentioned above with respect to Claims 17 and 23. Otsuka now says that blocking neurotransmission at dopaminergic receptors, as demonstrated by the animal testing reported in the '528 patent, is a utility that supports Claim 12. The '528 patent (at Col. 1:59-61) does mention "strong activity for blocking neurotransmission of dopaminergic receptor," but it is mentioned *only* as *an activity* of the compound in animal testing and *not* as *an actual use* for it in humans. A mere *activity* is *not* necessarily a *practical* utility, and a "practical" utility is what the law requires. *In re Fisher*, 421 F.3d 1365, 1371 (Fed. Cir. 2005); *Ziegler*, 992 F.2d at 1200-01; *Eli Lilly v. Actavis*, 676 F. Supp. 2d at 366. A "practical" utility is a "real world" utility that has "a significant and presently available benefit to the public." *Fisher*, 421 F.2d at 1371.

A few examples will show that not just any activity is sufficient to meet the utility requirement. In *Rey-Bellet v. Engelhardt*, 493 F.2d 1380, 1384-85 (C.C.P.A. 1974), success in

the tetrabenazine antagonism test did not establish a practical utility because (a) it was insufficient to establish antidepressant activity in man (which would have been a "practical" utility) and (b) it was not shown that "the property of tetrabenazine antagonism is per se useful." In *Huang v. Prasit*, Pat. Interference No. 104,134, 2002 WL 226995, at *12 (B.P.A.I. 2002), the compound had "good COX-2 inhibitory selectivity." That was not enough to amount to a "practical" utility. *Id.* at *14-16. The losing party had argued "anti-inflammatory activity" as its practical utility. *Id.* at *13. But the COX-2 inhibition test results it submitted were insufficient to establish such anti-inflammatory activity. *Id.* at *14, *16. In *Hoffman v. Klaus*, 9 U.S.P.Q.2d 1657, 1658 (B.P.A.I. 1988), testing established that "the compound was active as an inhibitor for production of collagenase." But that was not itself a practical utility. *Id.* ("[T]here is no pharmaceutical marketed with the approved indication that it is useful for inhibiting collagenase production . . . ."). Although treatment of arthritis would have been a practical utility, the collagenase test results in that case were insufficient to establish usefulness against arthritis. *Id.* at 1658-59.

Hoffman explains that the key is not whether the compound has activity *per se*, but whether the activity shown by the tests is sufficient to prove the compound has an otherwise useful purpose in the treatment of specific diseases. 9 U.S.P.Q.2d at 1660. In the *Fisher* case, the Federal Circuit distinguishes other cases on this very ground. 421 F.3d at 1377 ("In *Jolles*, *Nelson*, and *Cross*, the applicants disclosed specific pharmaceutical uses in humans for the claimed compounds and supported those uses with specific animal test data, *in vitro*, *in vivo*, or both.") (emphasis added).

There is no evidence, or even argument by Otsuka, that blocking of neurotransmission at dopaminergic receptors is of itself a "specific pharmaceutical use in humans." *Id.* Rather, the

relevance of dopaminergic blockage in the animal test results is an indicator of antischizophrenic potential in humans. But, per Otsuka, the alleged "failure" of OPC-4392 in human testing trumps animal testing, and so Otsuka's dopaminergic blockade argument for Claim 12 puts it right back in the same dilemma it has with respect to Claims 17 and 23.

In fact, OPC-4392 was not the abject failure that Otsuka makes it out to be. But if Otsuka's position were to be accepted by the Court, then the legal consequence would be invalidity of the asserted claims under §§ 101/112 for lack of enablement.

H. THE STEREOTYPY DATA IN THE HIROSE DECLARATION WERE BIASED AND CONFOUNDED AND THUS CANNOT SUPPORT ANY UNEXPECTED RESULTS.

The PTO relied on the stereotypy data in the Hirose Declaration as the basis for allowing the '528 patent to issue from the reexamination. But these data are unreliable and cannot support any unexpected results because (1) the stereotypy protocol had a confound and (2) the stereotypy observers were potentially biased to produce superior data for aripiprazole. (Beninger 929:11-21.)

1. *The Stereotypy Scale Is Not an Objective Scale.*

The problems of the confound and bias arise from the subjective nature of the stereotypy scale. The stereotypy scale of the Hirose Declaration required the observers to correlate mouse behavior to one of the four following scores:

> Score 0: Absence of stereotypy or any *abnormal* movement
> 1: *Slight* stereotyped head movements and *intermittent* sniffing
> 2: *Intense* head movements and *mild* licking *interspersed* with sniffing
> 3: *Intense* licking and/or gnawing.

(Beninger 938:15-939:20; DTX 399, Ex. 1 at 9 (emphasis added).) It does not take a scientist to recognize that this scale is not objective.

The field of behavioral pharmacology also recognized the scale's subjectivity.[7] In a book entitled METHODS IN BEHAVIOURAL PHARMACOLOGY, Drs. Ellenbroek and Cools explain that "[stereotypy] rating scales are *very subjective*. Even experienced raters will find it difficult to objectively distinguish between instances of different activities such as occasional licking and continuous licking affecting interrater reliability (defined as the degree of agreement between two different raters of the same sequence of stereotyped behaviour." (DTX 537 at 524 (emphasis added).) In the journal of NEUROSCIENCE AND BIOBEHAVIORAL REVIEWS, Drs. Rebec and Bashore note that "[a] further problem with rating scales is that they are *subjective*. Even if observers are 'blind' to the treatment conditions of individual animals, they are still *required to make personal judgments* about which of several categories of a given rating scale best describes the behavior being expressed at a certain time after drug injection. This uncertainty leads to variability not only between different observers using the same rating scale, but also between different rating scales used by different laboratories." (DTX 529 at 155 (emphasis added) (citation omitted).) And in the journal of PSYCHOPHARMACOLOGY, Dr. Fray et al. state that "ratings, even if made blind, are nevertheless *subjective* . . . . Thus, rating scales demand that the observer not only judge whether a particular response has occurred, but also assess its stereotypic nature. This complexity sometimes leads to confusion in rating, even among experienced observers . . . ." (DTX 411 at 253 (emphasis added).)

Otsuka's tortured attempts to argue that the scale is objective are untenable. First, Dr.

[7] The field not only criticized the problems that can arise from the subjective nature of the stereotypy scale, but it also sought to develop tests with objective scoring, such as the mouse jumping test. (*See, e.g.*, DTX 375 at 669 ("[M]easurement techniques employed to assay amphetamine stereotypy in experimental animals are often based upon subjective signs and, therefore, a precise quantitation of the end point is less likely to be achieved. Moreover, a trained observer is always required to score stereotypy and the recording of it cannot be automated. . . . We, therefore, undertook to determine if blockade of mouse jumping can be used as a sensitive and specific test for the neuroleptic drugs.").)

Roth resorted to "semantics," claiming that the scale is objective because observers do not "ask[] the mouse to tell us what their degree of stereotypy is." (Roth 1116:7-22.) Dr. Roth, however, backed away from this strained definition and acknowledged that the scale may be considered subjective in the neuropharmacological field even though the test did not fit his definition of "subjective." (Roth 1116:7-22.) Furthermore, before he was signaled by an audience member, Dr. Hirose testified that the scale is subjective. (Hirose 1936:2-1937:5.) Otsuka claims that Dr. Hirose's testimony was incorrectly translated; however, Dr. Hirose's statement in response to a prior question that observers must "subjectively" correlate behavior to a numerical score on the scale was neither retranslated nor corrected. (Hirose 1935:21-1936:1.) Finally, Otsuka's attempt to explain away the subjectivity of the scale by arguing that each score has a unique "combination" of behaviors is not credible. (OFFCL at 137 n.2.) In an attempt to illustrate these alleged unique combinations of behaviors, Dr. Hirose offered no reason for modifying the scale by removing its adjectives and otherwise rewording it. (Hirose 1937:8-1938:6.) For example, Dr. Hirose replaced "mild licking" with simply "licking" for a score of 2. (Hirose 1937:11-1938:6; DTX 399, Ex. 1 at 9.) According to the scale, though, behavior should not be scored a 2 unless it exhibits "mild licking." (DTX 399, Ex. 1 at 9.) Otherwise, the scale would say just "licking" and would not distinguish between "mild" and "intense" licking in scores of 2 and 3. (DTX 399, Ex. 1 at 9.) Moreover, if Dr. Hirose had used a modified scale to score the mice for the Hirose Declaration, he should have informed the PTO, as an examiner would have expected the plain language of the scale to have been followed. Dr. Hirose's testimony in this regard is even more implausible in light of the three articles that describe the scoring scale as "subjective" and the fact that Otsuka offered no explanation for why they should be disregarded in favor of Dr. Hirose's self-serving statements. (DTX 411 at 253 ("First, ratings, even if made blind, are

nevertheless subjective."); DTX 529 at 155 ("A further problem with rating is that they are subjective. Even if observers are 'blind' to the treatment conditions of the animals, they are still required to make personal judgments . . . ."; DTX 537 at 524 ("Secondly, rating scales are very subjective.").)

2. *The Stereotypy Protocol Had a Confound and Thus the Data Cannot Support Unexpected Results.*

Otsuka does not challenge Defendants' evidence that Dr. Hirose scored the mice for aripiprazole and Dr. Kikuchi scored the mice for the 2,3-dichloro propoxy. As Dr. Beninger explained, because one cannot tell whether the difference in scores between aripiprazole and the 2,3-dichloro propoxy is attributable to the compounds themselves or to the observers, a confound exists that renders the data uninterpretable. (Beninger 938:1-14.) A confound that is built into the data by flawed methodology cannot be eliminated. (Beninger 945:21-946:7.) Otsuka does not challenge that the protocol contains a confound, and its attempts to circumvent this fact by contending that there is no evidence that the data are confounded fail.

First, Otsuka claims that using multiple observers is not inappropriate and can reduce so-called "rater fatigue." (OFFCL at 145.) Defendants do not argue that using multiple observers is intrinsically wrong; rather, Defendants argue that having both the observers and the compounds change systematically together results in a confound. (Beninger 938:1-14.) Moreover, Dr. Roth presented no literature indicating that rater fatigue can be a problem when observing stereotypy. Nor is this argument credible in light of the fact that on any given day an observer scored mice for only one compound. (Thisted 1459:4-9; 1470:9-11; *see generally* DTX 285-T.)

Second, Otsuka argues that because Drs. Hirose and Kikuchi showed good inter-rater reliability when scoring mice that received no test compounds, Drs. Hirose and Kikuchi necessarily showed good inter-rater reliability when scoring mice that actually received test

compounds. (*See* OFFCL at 145-47.) Otsuka's experts cannot support such a sweeping proposition. As Dr. Beninger explained, statistical analyses involving only the control mice cannot eliminate the concerns of a confound, because "it remains unknown" whether the observers differed in their scoring of mice that actually received test compounds. (Beninger 946:2-17.) This testimony—that a statistical analysis cannot include the scores of the mice that actually received test compounds—is unchallenged. Both Drs. Roth and Thisted agreed that their inter-rater reliability analyses only looked at the inter-rater reliability in the observations of the mice that received no test compound, and could not be performed on observations on mice that actually received test compounds. (Roth 1305:16-1306:7; Thisted 1500:21-1501:2.)

Otsuka's argument that because some control mice were assigned scores of 1, 2, and 3, an analysis of the control mice provides information on how the observers assigned scores of 1, 2, and 3 is misleading. (*See* OFFCL at 147.) What score the control mice were actually given is irrelevant since there is no way to compare those scores to the actual behavior of the mice. (Thisted 1484:21-1485:1.) It will remain unknown whether the mice that actually received test compounds were scored by Drs. Hirose and Kikuchi the same way, because one cannot directly compare Dr. Hirose and Dr. Kikuchi's scoring of treated mice. Further, any review or statistical analysis of the stereotypy data and dose-response curves by Dr. Roth holds no weight as he provided no proof whatsoever of his alleged calculations performed to reach his conclusion. (Roth 1311:6-10.)

Otsuka also claims that because Dr. Kikuchi trained Dr. Hirose and that they routinely performed stereotypy testing, one would expect a high degree of inter-rater reliability. (*See* OFFCL at 145, 147.) Such unsupported anecdotes are not persuasive. Otsuka has not provided any documentary evidence that Drs. Kikuchi and Hirose performed stereotypy tests together

around the time of the reexamination, nor has it proffered any documentary evidence that Drs. Kikuchi and Hirose ever had a high degree of inter-rater reliability.

Finally, Otsuka's argument that the "overall study" incorporated a so-called "balance" and somehow rectified the situation is misleading, incorrect, and irrelevant. (*See* OFFCL at 146.) According to Otsuka, because Dr. Hirose scored the mice for two claimed compounds and two prior art compounds, and because Dr. Kikuchi scored the mice for two claimed compounds and two prior art compounds, any difference in scoring between Drs. Hirose and Kikuchi would have been "balanced." As an initial matter, Otsuka's expert Dr. Thisted cited no literature and gave no rationale in support of this theory. More importantly, the Hirose Declaration does not compare all the claimed compounds to all the prior art compounds; rather, Dr. Hirose carefully states that comparisons could only be made between the claimed compound and its propoxy homolog:

> The comparisons that could be made are:
>
> Test Compound 1 versus Test Compound A;
>
> Test Compound 5 versus Test Compound B;
>
> Test Compound 6 (HCl) versus Test Compound C (HCl); and
>
> Test Compound 8 versus Test Compound D.

(DTX 399 at 9.) Because all the claimed compounds as a group are not compared to all the prior art compounds as a group, the fact that Drs. Kikuchi and Hirose alternated scoring the test compound in each of the comparison pairs is irrelevant.

3. *The Stereotypy Data Are Potentially Biased and Thus Cannot Support Unexpected Results.*

As with the confound issue, Otsuka cannot escape important basic facts—in this case that Drs. Hirose and Kikuchi knew the identity of the test compounds and knew that the Hirose

Declaration sought to demonstrate the alleged superiority of aripiprazole. As with the confound, Otsuka's attempt to overcome the bias in the data suffers from the fatal flaw in the statistical analyses of Drs. Roth and Thisted: that both analyses only looked at observations of the mice that received no test compound, and did not analyze observations of the mice that actually received test compounds. (Roth 1305:16-1306:7; Thisted 1500:21-1501:2.) As Dr. Beninger testified, statistical analyses involving only the control mice cannot eliminate the concerns of a bias, because "it remains unknown" whether the observers differed in their scoring of mice that actually received test compounds. (Beninger 946:2-17.) This testimony—that a statistical analysis cannot include the scores of the mice that actually received test compounds—remains uncontroverted. In fact, there is no way to tell whether the data are biased because one cannot review the individual scores and determine whether Drs. Hirose or Kikuchi actually scored the mice correctly or whether they biased the data. (Thisted 1484:21-1485:1.)

Otsuka's further arguments that the randomization of doses and the normalization of data guard against the potential for bias are also unavailing. (*See* OFFCL at 148-51.) Both of those arguments assume that the bias would skew the data in the same way for all mice—ones that received the test compound and ones that received no test compound. However, Dr. Beninger explained that an experienced observer would understand when he was scoring the control mice, and thus bias could not affect those scores as much as it might affect other scores. (Beninger 943:25-944:18; 954:22-955:10.) Otsuka argues that because not all the control mice received the same scores that Dr. Beninger's critique is flawed. (*See* OFFCL at 151.) This argument mischaracterizes Dr. Beninger's testimony and ignores the fact that any test involving animals will naturally have some variability, and thus one could expect the control mice to exhibit some variable behavior; in fact, six mice were used at each dosage level to help control for this natural

variability. (Thisted 1446:8-1447:18.)

4. *The Confound and Potential for Bias Could Have Easily Been Avoided.*

Dr. Beninger suggested modifications to the stereotypy protocol that would have avoided the confound and potential for bias. Rather than address the substance of these suggestions, Otsuka claims that such modifications were "unnecessary" or introduce a "substantial level of complexity." (OFFCL at 152.) Dr. Beninger, however, explained that his proposed modifications are necessary to avoid the potential for bias and the confound that are inherent in the stereotypy protocol. (Beninger 945:21-946:7.) Dr. Thisted's testimony that adding a third person could have introduced additional errors and variability is unsupported by any rationale or documentary evidence, and is therefore unconvincing.

Recognizing that its arguments are strained, Otsuka also attempts to reargue its failed *Daubert* motion and attacks Dr. Beninger's credentials. (*See* OFFCL at 23, 151.) Otsuka's characterizations are incorrect and misleading. Stereotypy testing, from designing the protocols to observing and analyzing the data, is unquestionably within Dr. Beninger's expertise. (Beninger 921:9-23.) Further, Dr. Beninger's expertise directly relates to schizophrenia in both the pharmacological and clinical settings. He has taught psychiatric residents about dopamine, schizophrenia, and the possible mechanisms of antischizophrenic medications, has given lectures to pharmaceutical companies about schizophrenia, and has been involved both in research involving schizophrenic patients and in evaluation of antischizophrenic agents. (Beninger 918:5-919:14.)

Otsuka also makes much of the fact that Dr. Beninger did not himself statistically analyze the stereotypy data. But Dr. Beninger clearly explained that a statistical analysis could not eliminate the concerns regarding the confound or potential bias. (Beninger 946:2-17; 955:11-20.) Therefore, any statistical analysis by Dr. Beninger would have been pointless. Otsuka's

further contention that Dr. Beninger should have performed stereotypy testing to support his position is also irrelevant. It is Otsuka's burden to show unexpected results.

Finally, Otsuka's argument that Dr. Beninger has himself published stereotypy results from other laboratories does nothing to undercut Dr. Beninger's opinions. (*See* OFFCL at 142; PTX 459.) Dr. Beninger did not impugn the stereotypy test *per se*. He challenged the specific protocol that Dr. Hirose used to conduct the stereotypy test: because the protocol in the Hirose Declaration had built into it a confound and potential for bias, the stereotypy data obtained was uninterpretable and could not be used to demonstrate that one compound was superior to another.

III. DEFENDANTS HAVE CARRIED THEIR BURDEN WITH RESPECT TO INEQUITABLE CONDUCT.

Otsuka's main arguments against a finding of inequitable conduct are that Defendants have not named individuals as the perpetrators of inequitable conduct, that the withheld information was not material, and that Defendants have not proved intent. Plaintiff attempts to obfuscate the issues on all three points, and none of its arguments should prevail.

A. DRS. OSHIRO, HIROSE AND MR. VAN HORN OWED A DUTY OF CANDOR TO THE PTO.

Contrary to Otsuka's contention, Defendants have accused specific individuals of inequitable conduct: Dr. Oshiro (the principal inventor who was also substantively involved with the reexamination of the '528 patent), Dr. Hirose (who prepared and submitted the Hirose Declaration during the prosecution of the reexamination) and Mr. Van Horn (who prosecuted the reexamination of the '528 patent). (*See* DFFCL at 69, 71-72, 159-60.) There can be no dispute that each of these individuals is a person who owed a duty of candor to the PTO. 37 C.F.R. § 1.56(a)(1)-(3). (*See* DFFCL at 145, 149, 151-52, 156.)

B. THE WITHHELD INFORMATION WAS HIGHLY MATERIAL.

Contrary to Otsuka's contention, the withheld information was highly material.

1. *The Inconsistent Internal Stereotypy Data.*[8]

Otsuka argues that the inconsistent stereotypy data is not material because Defendants did not ask Dr. Oshiro whether this data was inconsistent. (*See* OFFCL at 161-62, 227-28.) First, the internal data is on its face inconsistent with the data submitted to the PTO in the Hirose Declaration. The internal data clearly shows a six-fold difference in potency between aripiprazole and its propoxy homolog, while the data in the Hirose Declaration shows a 23-fold difference. (*See* DFFCL at 73-74.) At trial, Dr. Oshiro admitted that he obtained this data in 1987 and admitted that this internal data showed only a six-fold difference in potency between aripiprazole and its propoxy homolog. (Oshiro 1899:23-1903:7; DTX 59-T; TDX 51.) The Hirose Declaration was crucial evidence that convinced the reexamination examiner that a change from the propoxy to the butoxy linker yielded "unexpected" superiority. (*See* DFFCL at 69-72; DTX 121 at 01412; Goolkasian 527:12-20.) Data showing a difference in potency between aripiprazole and its propoxy homolog of six fold rather than 23 fold would certainly have been considered important to the examiner in deciding whether to confirm the patentability of the '528 patent. Therefore, the inconsistent internal stereotypy data was highly material. (*See* DFFCL at 148-49.)

Second, this inconsistency is even more material because at trial, for the first time, Dr. Oshiro testified that he did not consider a six-fold difference to be a considerable or surprising difference. (Oshiro 1772:12-1773:18; 1843:21-1844:7.) Otsuka's attempts to obfuscate this admission are unavailing. During his direct examination, Dr. Oshiro lucidly recalled experiments done in the late 1980s for the development of aripiprazole. One of these

[8] As explained in Defendants' Opposition to Otsuka's Motion to Strike New Arguments Raised for the First Time in Defendants' Proposed Findings of Fact and Conclusions of Law, Defendants have raised no new inequitable conduct arguments involving omitted internal stereotypy data after trial.

experiments was the comparison of OPC-4392 to its butoxy homolog. Dr. Oshiro clearly and without hesitation testified that the result obtained was not considerable or surprising:

> We did not find a considerable increase in the activity such as when we say from 4310 to OPC-14542. In other words, even if the propoxy was changed to butoxy, we did not see a surprising increase, such as a 15-fold increase.

(Oshiro 1772:24-1773:3.) Otsuka's attempt to edit this testimony to essentially read "[w]e did not find . . . a 15-fold increase [when changing OPC-4392 to its butoxy homolog]" is wishful thinking. (*See* OFFCL at 227-28.) During his cross-examination, Dr. Oshiro was reminded of the statement he made on direct and admitted that the not considerable and unsurprising difference was a six-fold difference. (Oshiro 1844:2-1845:9; PTX 37-T.) Otsuka argues that Dr. Oshiro's testimony cannot be so interpreted because Defendants did not in addition ask whether this was the data he was referring to or ask to specifically identify the data he was referring to. (*See* OFFCL at 161-62, 227-28.) If Otsuka believed that Dr. Oshiro's testimony was unclear or incorrect, it had the opportunity to object or clarify it on redirect. Otsuka cannot now hypothesize that maybe Dr. Oshiro was referring to some different data or the data was not inconsistent for some unknown reason.

Otsuka also notes that no evidence was presented regarding the test conditions underlying the internal stereotypy data. (*See* OFFCL at 227.) The Federal Circuit, however, has found that the absence of information on test conditions does not detract from the materiality of inconsistent internal data. *See Cargill, Inc. v. Canbra Foods, Ltd.*, 476 F.3d 1359, 1365-66 (Fed. Cir. 2007) ("Cargill argues that the data contained in the 1992 Report is not material because the tests underlying the Report were performed under unusual conditions and, thus, are not comparable to the data submitted to the examiner. . . . Cargill also contends that, because the Oven Data does not set forth any testing conditions, it too cannot be compared with the data before the examiner.

Even accepting as true the factual premises of those arguments, the documents withheld during prosecution remain material.")

2. *False Statements in the Hirose Declaration.*

Otsuka does not state that the protocol submitted to the PTO accurately reflects the test methods used by Dr. Hirose in carrying out the stereotypy tests; rather, Otsuka argues that Defendants did not prove that the protocol did not accurately reflect those test methods. (*See* OFFCL at 232-33.) Otsuka is wrong. Again, Defendants have shown that on its face the protocol submitted to the PTO does not accurately reflect the test methods used by Dr. Hirose. (*See* DFFCL at 152-54.) Otsuka's attempts to avoid the clear language of the protocol are strained and unconvincing. First, Otsuka invokes a novel interpretation of the statement and claims that the meaning of the phrase "observation for stereotyped behavior will be performed by an observer blind to the treatment received by the mice" indicates only that "individual mouse observations would be performed by a single individual." (OFFCL at 164-65.) There is no basis in the trial testimony or the protocol for this newly minted interpretation, and it is clearly contradicted by the trial testimony. (Beninger 932:1-7; 957:18-958:8.) Otsuka's arguments that the examiner would have understood that the observations were conducted by more than one observer because the protocol identifies two investigators, and that the examiner would have understood the phrase "an observer blind to the treatment received by the mice" to mean that the observer was blinded to the dosage but not the compound with which the mice were treated are equally unavailing for the reasons discussed in Defendants' Findings of Fact and Conclusions of Law. (*See* DFFCL at 77-80, 152-54). Finally, that Dr. Hirose employed the standard method used at Otsuka to obtain data submitted to the FDA is irrelevant. This does not make the Hirose Declaration protocol accurate.

3. *The Nakagawa Declaration.*

Contrary to Otsuka's contention, ample evidence at trial showed that the Nakagawa Declaration does teach that antipsychotic activity increases when the linker in the carbostyril is changed from a propoxy to a butoxy. As discussed above in Section I(B)(2), Otsuka provided no contradictory evidence. Thus, the Nakagawa Declaration was highly material to the reexamination of the '528 patent.

Otsuka's arguments that the data in the Nakagawa Declaration cannot be compared with the data in the Hirose Declaration, that there is no scientific correlation between the two tests, and that the mouse jumping test has never been used to develop a new antipsychotic drug, even if true, are beside the point. Defendants have shown that the mouse jumping test is a valid test for determining antipsychotic activity and the data in the Nakagawa Declaration shows that antipsychotic activity increases when the linker is changed from propoxy to butoxy. (*See* Sections II(A)(1) & II(C), I(B)(2) & II(A)(2).) Otsuka's argument that the the Nakagawa Declaration does not show superiority of all butoxy compounds because it only shows superiority of the unsubstituted butoxy over the unsubsituted propoxy is specious. Defendants provided ample evidence that one of ordinary skill in the art having this data would have a reasonable expectation that antipsychotic activity increases when the only change in the molecule is the extension of the linker from a propoxy to the butoxy. This is exactly what Otsuka was trying to prove with the Hirose Declaration. In addition, as discussed above in Sections I(B)(2) and II(C), contrary to Otsuka's contentions, the data in the Nakagawa Declaration is amply sufficient to support the conclusions that Defendants draw from it, and teaches to modify (not away from modifying) the unsubstituted butoxy to make aripiprazole.

Finally, Otsuka's new theory that the Nakagawa Declaration is not relevant because the Banno article was before the PTO is nonsensical. (*See* OFFCL 169-70, 236.) The Banno article

is not prior art on its face and was not published until November 1988. (DTX 84). Furthermore, the Banno article does not contain the Nakagawa Declaration data regarding the unsubstituted butoxy, which is also contained in Otsuka's 1979 internal status report. (DTX 208, DTX 208-T; Oshiro 1868:12-1869:17). Otsuka's disclosure of the Banno article, which is not prior art, does not change the fact that Otsuka did not disclose the Nakagawa Declaration, which contained relevant comparative test data showing the unsubstituted butoxy was more potent than the unsubstituted propoxy homolog.

4. *False Statements During the Reexamination of the '528 Patent.*

Otsuka does not contend that the statements in question are not material. Rather, it contends that its statements in the reexamination—arguing that there was no evidence that the five exemplary carbostyril derivatives of the '416 patent had antischizophrenic activity—were not false because Otsuka's statement was limited to the disclosures in the references cited by the examiner. (*See* OFFCL at 172-73, 238-40.) Again, Otsuka misconstrues the evidence. Otsuka's statement does not say that the prior art references do not contain evidence that the five exemplary carbostyril derivatives had antischizophrenic activity. It clearly states that no such evidence exists:

> [W]hile these references may suggest that their compounds may be useful for treating central nervous disorders, *there is no* evidence that the five exemplary compounds identified by the Examiner have such properties let alone the recited property of treating schizophrenia.

(DTX 121 at 01274.) Furthermore, this statement, and Defendants' understanding of it, was cited by multiple witnesses at trial. Otsuka had the opportunity to challenge its meaning by calling Mr. Van Horn but decided not to do so.

Regardless of the context of these statements, however, the data generally refutes the position Otsuka took in opposing the examiner's argument for unpatentability and asserting an

argument for patentability, and is therefore material. 37 C.F.R. § 1.555; 37 C.F.R. § 1.56; *Cargill*, 476 F.3d at 1367 ("Even if there were a mitigating explanation for the withheld data, it was no excuse for the applicant's purposeful omissions in this case. 'Close cases should be resolved by disclosure, not unilaterally by the applicant.'" (quoting *LaBounty Mfg., Inc. v. U.S. Int'l Trade Comm'n*, 958 F.2d 1066, 1076 (Fed. Cir. 1992))).

C. DEFENDANTS HAVE ESTABLISHED INTENT.

Otsuka contends that Defendants have not proved intent because courts have found the intent requirement of inequitable conduct to be met when the inference of intent is "the single most reasonable inference able to be drawn from the evidence." *Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 537 F.3d 1357, 1366 (Fed. Cir. 2008). However, the Federal Circuit has repeatedly emphasized that "[i]ntent need not be proven by direct evidence; it can be inferred from indirect and circumstantial evidence." *Id.*; *see, e.g., Taltech Ltd. v. Esquel Enters. Ltd.*, 604 F.3d 1324, 1332 (Fed. Cir. 2010). Furthermore, in some instances, courts have held the patentee's failure to offer a credible explanation for its nondisclosure of highly material information may allow the court to draw an inference of intent. *See, e.g., Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd.*, 394 F.3d 1348, 1354-55 (Fed. Cir. 2005) (affirming the district court's finding of inequitable conduct and drawing an inference of deceptive intent in view of the high materiality of the undisclosed information).

In this case, the false statements and suppressed information are highly material because they contradict the information that secured the allowance of the reexamination certificate. Given the high degree of materiality, Defendants' circumstantial evidence is sufficient to draw an inference of intent. (*See* DFFCL at 158-61.)

1. *Dr. Oshiro.*

Otsuka contends that Defendants have not proven intent on the part of Dr. Oshiro because

he did not affirmatively testify that he was aware of the test data submitted in the Hirose Declaration and therefore could not have known that there was a contradiction between that data and Otsuka's internal data. Otsuka has again misconstrued the trial testimony. Otsuka claims that Dr. Oshiro "merely testified that 'most likely this draft – draft of this declaration was sent to me as an attachment to an e-mail requiring or requesting me to check the wording for the way things are worded in the document." (OFFCL at 163, 229; Oshiro 1896: 21-1897:4.) In the portion of Dr. Oshiro's answer that Otsuka left out, Dr. Oshiro clearly testified that he recalled reviewing the draft declaration and providing comments: "So I recall writing up my review results and responded or sent back – sent him back an email." (Oshiro 1897:5-6.) There was therefore nothing uncertain about Dr. Oshiro's substantive involvement in the preparation of the Hirose Declaration. One would expect that by the time Dr. Oshiro was asked to review the declaration, the test data was in it. If this expectation were incorrect, Otsuka should have clarified on redirect, but it did not.

Furthermore, the record is clear that Dr. Oshiro was extensively involved in the reexamination. He was part of the core group at Otsuka entrusted with the reexamination of the '528 patent and was involved in meetings relating to the reexamination. (Hirose 1914:9-21; Oshiro 1874:1-11; Van Horn Dep. 116:14-117:6.) In fact, Dr. Oshiro is listed on some 60 communications on Otsuka's privilege log between the time of the January 15, 2005 Office Action and May 16, 2005, when Otsuka filed its response submitting the Hirose Declaration. (Oshiro 1879:25-1880:19; DTX 61-A at entry nos. 63-127.) It is inconceivable that he would not have been aware of the data submitted in the Hirose Declaration. The fact that Otsuka did not redirect him on this point further confirms that he was.

Otsuka's arguments that Defendants did not prove that Dr. Oshiro was aware of the

contradictory internal stereotypy data in 2005 are also beside the point. Dr. Oshiro showed no surprise or trouble recalling the data when he was confronted with it during his cross-examination. (Oshiro 1814:16-1815:2; 1901:2-7.) There is no reason to believe that he was not aware of it in 2005 as well. Again, the fact that Otsuka did not redirect him on this point confirms that he was. Therefore, Otsuka's contention that Defendants did not prove intent because they did not inquire whether Dr. Oshiro believed there was a contradiction is equally unpersuasive.

Finally, Otsuka had the opportunity on redirect to inquire of Dr. Oshiro whether there was a contradiction between the internal data and the data submitted to the PTO, and whether he intentionally withheld that information, but did not do so. Nor did it provide any witness to explain the contradiction in the data. This adds to the circumstantial evidence that justifies an inference that Dr. Oshiro knew of the inconsistent stereotypy data and intentionally did not disclose it to the PTO.

2. *Dr. Hirose.*

Otsuka cannot deny the materiality of the Hirose Declaration. Rather, Otsuka contends that Defendants have not proven intent on the part of Dr. Hirose because he had followed the procedure described in the declaration's protocol on many occasions and had used the procedure to generate data for submission to the FDA. (*See* OFFCL at 232-33.) Whether Dr. Hirose had followed the same procedure he used to produce internal Otsuka data for submission to the FDA is irrelevant. The examiner would not have been aware of these procedures or whether Dr. Hirose had followed them when performing the tests for his declaration. (Beninger 958:9-13; 958:17-20; Thisted 1503:16-24.) The examiner's understanding of the procedure would have been based on a plain reading of the protocol. As a declarant and a crucial member of the team responsible for Otsuka's reexamination, Dr. Hirose had a duty to disclose information that would

have been considered important to the examiner—namely, how the experiments were actually carried out. (Goolkasian 524:3-18.) In light of the years spent working on the reexamination, Dr. Hirose's bias to produce superior results for aripiprazole, and the high materiality of the Hirose Declaration, the single most reasonable inference is that Dr. Hirose intended to mislead the PTO. (Hirose 1916:2-17; 1976:11-1981:19.)

3. *Mr. Van Horn.*

As discussed in Defendants' Findings of Fact and Conclusions of Law, it is inconceivable that the persons involved with the filing and prosecution of the reexamination application, including Mr. Van Horn, were not aware of the Nakagawa Declaration and the data it contains regarding two of the exemplary compounds cited by the examiner. The high level of materiality of the withheld information together with Mr. Van Horn's absence at trial justify an inference that Mr. Van Horn was aware of the documents and that he withheld them from the PTO with intent to deceive. Otsuka's main argument is that Federal Circuit law holds that "[a]n unfavorable inference may not be drawn from the lack of testimony by one who is equally available to be called by either party." (OFFCL at 237 (quoting *A.B. Dick v. Burroughs Corp.*, 798 F.2d 1392, 1400 n.9 (Fed. Cir. 1986).) Otsuka misconstrues the case. In that case, the Federal Circuit affirmed inequitable conduct and noted that the district court could have drawn a negative inference of deceptive intent from the absence of the prosecuting attorneys at trial:

> When a party knows of witnesses on a material issue and they are within his control to produce, if the party chooses to not call the witnesses, the fact finder may draw the inference that the testimony would have been unfavorable.

A.B. Dick, 798 F.2d at 1400 n.9 (citations omitted); *see also Wilsa, Inc. v. Syntex (U.S.A.) Inc.*, 856 F.2d 202, 1988 WL 85239, at *1 (Fed. Cir. Aug. 18, 1988) (unpublished) (citing *A.B. Dick* for the same proposition). The language Otsuka quotes is explained as a generalization which does not apply where, as in this case, the likelihood of bias of the potential witness is great. *A.B.*

Dick, 798 F.2d at 1400 n.9. In those cases the witness is not considered to be equally available to both parties. *Id.*

In *A.B. Dick*, the Federal Circuit explained that the party charged with inequitable conduct "would naturally have been expected to call . . . [the prosecuting attorney] if his testimony on the reasonableness of his conduct would have been favorable to it, or to explain why it did not do so." 798 F.2d at 1400 n.9. Mr. Van Horn is in the same position as the prosecuting attorney in *A.B. Dick*. Otsuka would naturally have been expected to call Mr. Van Horn if his testimony on the reasonableness of his conduct would have been favorable, or to explain why it chose not to call him. As the Federal Circuit has explained, "[n]ormally, it can be expected that an innocent party will be motivated to try to present convincing reasons for its actions or inaction." *Bruno*, 394 F.3d at 1354. Instead, Otsuka waited until the eleventh hour to notify Defendants that it was not calling Mr. Van Horn as a witness at trial and did so only when Mr. Van Horn was not in the courtroom and thus unavailable to Defendants. Therefore, the court may draw an adverse inference based on Otsuka's decision to not call Mr. Van Horn.

IV. CONCLUSION.

For the reasons stated herein, and in Defendants' Post-Trial Proposed Findings of Fact and Conclusions of Law, the asserted claims of the '528 patent are invalid and the patent is unenforceable.

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Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on October 19, 2010, a true and correct copy of the foregoing DEFENDANTS' REPLY TO OTSUKA'S POST-TRIAL PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW was served upon counsel of record via e-mail:

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